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THE DIFFERENTIAL DIAGNOSIS OF CHRONIC BRIGHT'S DISEASE*

A Clinicopathological Correlation

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IT IS quite apparent to clinicians that the task of correctly foretelling the pathological findings in cases of advanced renal disease is difficult and may be impossible, since the end results of many types of renal disease may be similar so far as the clinical picture is concerned. Although much work on renal physiology and pathology has been reported in recent years, the studies that have approached the problem from the viewpoint of the clinician faced by a patient with hypertension and failing renal function are few in number, and those that have been made have for the most part paid little attention to chronic or healed pyelonephritis as an important type of chronic Bright's disease.

There exists, moreover, considerable confusion in the clinical and pathological nomenclature of Bright's disease, largely owing to the many different classifications of nephritis that have been in use. To some extent this is, as Christian[1] states, "more a matter of difference in words than in concepts." It is for the most part agreed that in one group vascular lesions predominate; in a second, diffuse inflammatory glomerular lesions are chiefly present; whereas in a third, degenerative changes in tubules and glomeruli are the outstanding features. A fourth type, however, also exists in which the lesions are mainly interstitial and originally infectious. Within recent years it has been shown and emphasized by Longcope and Winkenwerder,[2, 3] Peters, Laviettes and Zimmerman,[4] Butler[5] Weiss and Parker[6] and others that renal infection — that is, pyelonephritis — may ultimately result in hypertension, often of the malignant type, as well as in renal failure. These late sequelae may occur even when the original infection has subsided and healing has taken place.

The pathological findings as well as the clinical manifestations of the various types of Bright's disease have been described on numerous occasions,[1–4, 6–14] and no attempt will be made here to summarize the literature. Brief comment is, however, called for on the term "malignant hypertension," about which much confusion exists. As originally applied by Fahr,[10] "malignant nephrosclerosis" was the pathological description of the kidneys of patients dying of uremia in which hyperplastic endarteritis and necrotizing arteriolitis were present. Later the problem was approached primarily from the clinical angle, and Keith, Wagener and Kernohan[15] applied the designation "malignant hypertension" to a syndrome of severe hypertension with retinitis and papilledema, progressing rapidly to a fatal termination. Although many such patients died in uremia, some succumbed to cardiac failure or cerebral accident. The latter cases usually exhibited pathologically the same general type of renal lesion as that described by Fahr, but often to a less severe extent than those in which death was primarily due to renal failure.

It has been subsequently shown that malignant hypertension as seen clinically does not represent a single pathologic entity, but may occur as the terminal phase of benign essential hypertension, chronic glomerulonephritis or healed or chronic pyelonephritis, as well as rarely in conditions such as renal infarction and congenital polycystic kidneys.[6, 16, 17]

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Choice of Material

In the present analysis only the commoner types of chronic renal disease that often terminate in uremia are considered. No analysis has been made of the degenerative renal diseases, such as nephrosis and amyloid disease, of congenital anomalies, of renal tuberculosis or of obstructive lesions without infection.

The cases were originally selected from the autopsy files of the Boston City Hospital and represent consecutive cases of each type, with the exclusion of those in which the pathological diagnosis was not clear, those with some other major disease that might complicate the interpretation of the clinical picture, such as heart disease of other etiology, and those in which there were insufficient clinical data. An exception was made only in cases of decompensated benign nephrosclerosis, for in this group only those patients with benign nephrosclerosis dying in uremia were included, which of course left out the vast majority of patients with essential benign hypertension. The selection and classification were therefore made on the basis of pathological findings.

The clinical studies were such as might be expected to be made routinely on the wards of a large general hospital and varied in extent and probably in accuracy. A few patients were personally observed by us.

Classification

This study has been limited to the three commoner large groups of chronic nephritis, each of which has been subdivided in the following manner:

I. Glomerulonephritis
   a. Subacute
   b. Chronic

II. Nephrosclerosis
   a. Benign
   b. Malignant

III. Pyelonephritis
   a. Healed
   b. Chronic

Although the concept of glomerulonephritis is an old and broadly accepted one, it is probable that many of the lesions that were so diagnosed in the past would now be called some stage of pyelonephritis or malignant nephrosclerosis. The concept of glomerulonephritis should be restricted, in our view, to lesions in which the primary change is a diffuse involvement of the glomeruli by an active or healed inflammatory process. Cases with a prolonged course can be divided more or less into two stages, usually known as subacute and chronic, although the dividing line is not a sharp one. In Table 1 are given the gross and microscopical criteria used for such separation, as well as the characteristic features of the other renal lesions under discussion.

Nephrosclerosis includes that group of kidneys in which the first and fundamental change is an arteriolar sclerosis. It has been suggested by Arthur Ellis,[9] who bases his conception on the experimental work of Wilson and Byrom,[18] that these changes are probably the result rather than the cause of an associated hypertension. A similar point of view is taken by Dock,[19] who summarizes the arguments in its favor. There is, however, another school of thought that maintains that renal arteriolar sclerosis is the primary disease, the hypertension resulting from the renal ischemia. This is the belief of Scott,[20] and it is at least assumed by Goldblatt, Kahn and Lewis[21] in a summary of the treatment of experimental hypertension.

As a result of the renal arteriolar lesions, changes are produced in the kidney that may or may not, according to their degree, lead to renal decompensation. Pathologically the distinction between benign and malignant nephrosclerosis is made mainly on the basis of the type of arteriolar sclerosis present. In the benign form this is chiefly hyaline in type, the hyaline thickening of the wall leading to marked narrowing or even complete occlusion of the vessel. In malignant nephrosclerosis the arteriolar sclerosis is hyperplastic in type, the lumens being narrowed or occluded by a proliferation of cells, probably fibroblasts, between the muscularis and the endothelium. Necrosis of the wall with hemorrhage into it, polymorphonuclear infiltration and fibrin deposition (necrotizing arteriolitis) often occur but are not so pathognomonic of the condition as is the hyperplastic change. Other gross and microscopical criteria are given in Table 1.

Not uncommonly borderline cases with combinations of the features of benign and malignant nephrosclerosis are found. Most of these patients are between fifty-five and sixty-five years of age and clinically are usually considered as examples of the malignant form.

Our conception of pyelonephritis is essentially that of Weiss and Parker.[6] The important gross and histologic characteristics are given in Table 1. The vascular picture is somewhat complicated. As shown by Weiss and Parker, hyperplastic arteriolar sclerosis may be restricted to those areas where the inflammatory process was originally present.

In the cases associated with hypertension, however, arteriolar sclerosis, usually hyperplastic in type, is present not only in the scarred areas but throughout the kidneys and also in other organs of the body. This diffuse process is probably best explained as caused by the hypertension.

The separation of chronic pyelonephritis from healed pyelonephritis is not an easy one, particularly from the purely pathological standpoint. It depends on one's being able to find evidence of active infection still present in the lesions. Such evidence usually consists of the presence of leukocytes in the interstitial tissue or in the lumens of the tubules. Sometimes even organisms can be demonstrated.

Table 1. *Gross and Microscopic Characteristics of the Kidneys in Chronic Bright's Disease.*

Characteristics	Subacute Glomerulonephritis	Chronic Glomerulonephritis	Benign Nephrosclerosis	Malignant Nephrosclerosis	Healed Pyelonephritis	Chronic Pyelonephritis
Gross	Large or normal; pale yellow; smooth to granular.	Pale; contracted; granular.	Contracted; granular; prominent blood vessels.	Slightly contracted; mottled pale and red; petechial hemorrhages.	Coarsely scarred or very contracted and granular	Coarsely scarred or very contracted and granular; abscesses (?).
Microscopic:						
Involvement	Diffuse	Diffuse	Focal	Focal	Focal or diffuse	Focal or diffuse
Glomeruli	Fresh crescents; increased cellularity.	Old crescents; adhesions; fibrosis.	Normal to fibrosed	Normal, infarcted, necrotic or inflammatory	Reduced in number; pericapsular fibrosis.	Reduced in number; pericapsular fibrosis.
Tubules	Fatty degeneration	Atrophy and dilatation	Atrophy and dilatation	Hyaline droplets; fatty degeneration.	Thyroid-like areas	Thyroid-like areas, with polymorphonuclear leukocytes in some
Interstitial tissue	Edema; doubly refractile fat.	Fibrosis	Fibrosis	Perivascular lymphocytic infiltration	Fibrosis; lymphocytic infiltration.	Fibrosis: polymorphonuclear, lymphocytic and plasma-cell infiltration.
Blood vessels.	Hyaline or hyperplastic arteriolar sclerosis	Hyaline or hyperplastic arteriolar sclerosis	Hyaline arteriolar sclerosis; atherosclerosis of arteries.	Hyperplastic arteriolar sclerosis; necrotizing arteriolitis.	Hyaline or hyperplastic arteriolar sclerosis	Hyaline or hyperplastic arteriolar sclerosis

Results

Relative Incidence

Since the cases studied were a selected group, they are not indicative of the relative incidence of the various types of chronic Bright's disease. Healed pyelonephritis, as judged from the presence of old scarring of the kidney, is of common occurrence. A recent study of Kinney and Mallory,[22] as yet unpublished, based on 1000 consecutive postmortem examinations at the Boston City Hospital, indicates that it may occur in nearly 14 per cent of all persons. Many of these lesions were minor in degree, and in life the patients had few or no clinical manifestations referable to their kidneys. Nevertheless the number of patients who had disease of such degree as to lead to renal failure or significant hypertension exceeded the number with subacute or chronic glomerulonephritis, as has been pointed out by Weiss and Parker.[6]

Essential hypertension, of course, occurs with great frequency, but the number of cases classed as decompensated benign nephrosclerosis is less than the incidence of malignant nephrosclerosis.

Age at Death

It will be seen from Table 2 that subacute and chronic glomerulonephritis, malignant nephrosclerosis and healed pyelonephritis in this series are diseases of youth and early middle age.

Predisposing Factors

Infection appears to bear a definite relation to glomerulonephritis. All but 1 of the patients with subacute glomerulonephritis and 6 of those with chronic glomerulonephritis had scarlet fever, sore throat or some other respiratory infection preceding the onset of symptoms. On the other hand, a clear-cut history of acute glomerulonephritis or of acute pyelonephritis was rarely elicited in the patients with chronic glomerulonephritis and with healed or chronic pyelonephritis, respectively. A history of toxemia of pregnancy occurred in only 2 cases, both in the healed pyelonephritis group.

Abnormalities of the urinary tract were not found in any group except that of pyelonephritis. One patient with healed pyelonephritis had a unilateral renal calculus with some hydronephrosis. Of the 6 cases of chronic pyelonephritis 1 patient

showed unilateral renal calculus with hydronephrosis; 1, an infant of eight months, had hydroureters; and 1 had prostatic obstruction.

Known Duration of Renal Disease and of Hypertension

The known duration of renal disease and of hypertension as judged from the records is probably an inaccurate indication of their actual duration. Nevertheless, it is of interest. In benign nephrosclerosis, known hypertension was frequently diagnosed some years before renal disease, whereas in the other groups renal disease was diagnosed initially or the hypertension and renal disease were first observed at the same time.

The relatively short duration of the known disease in malignant nephrosclerosis is striking, only 1 patient living three years after a diagnosis was first made, and the rest dying within two years. The duration of disease in subacute glomerulonephritis is also usually short (one year or less), although 3 patients were known to have had the disease for two and a half, three and six years, respectively. In the other groups the known duration varied from a few months to many years.

Terminal Arterial Blood Pressure

Figure 1 shows the average range of blood pressure for each patient during his terminal illness. The marked hypertension, especially diastolic, was consistently seen in malignant nephrosclerosis and was often but not always encountered in benign nephrosclerosis and chronic glomerulonephritis. In subacute glomerulonephritis and in healed pyelonephritis the ranges of pressure were wide, whereas only 1 case of chronic pyelonephritis exhibited well-marked hypertension.

Retinal Findings

Retinal findings were variously described in the records. An attempt has been made to classify them in a general way according to the terminology of Wagener and Keith.[14] Grade 4 changes consist of papilledema, usually with other severe

TABLE 2. *Summary of Clinical Data, Chiefly Expressed as Frequency of Occurrence.*

Diagnosis	No. of Cases	Age at Death	Duration of Renal Disease or Hypertension	Predisposing Infections	Terminal Urine		
					++++ albumin	W. B. C.	R. B. C.
		yr.		%	%	%	%
Subacute glomerulonephritis	10	16–43 (mean, 30)	1 mo.–6 yr.	90	100	100	100
Chronic glomerulonephritis	10	21–46 (mean, 35)	6 mo.–13 yr.	60	70	100	67
Decomp. benign nephrosclerosis	11	48–80 (mean, 63)	1 mo.–12 yr.	18 (?)	0	100	33
Malignant nephrosclerosis	11	27–51 (mean, 42)	2 mo.–4 yr.	0	55	90	37
Healed pyelonephritis	11	24–92 (mean, 40)	1 mo.–30 yr.	18 (?)	45	80	30
Chronic pyelonephritis	6	2/3–77 (mean, 45)	6 mo.–20 yr.	0	50	100	84

Diagnosis	Nephrotic Syndrome	Anemia	Terminal Uremia	Terminal Blood Pressure	Papilledema	Hypertensive Encephalopathy	Cerebrovascular Accident	Heart Failure	Terminal Heart Failure
	%	%	%		%	%	%	%	%
Subacute glomerulonephritis	90	70	80	125/70–190/146 (mean, 170/100)	50	10	0	40	10
Chronic glomerulonephritis	30	100	100	200/110–260/160 (mean, 200/130)	29	38	30	60	60
Decomp. benign nephrosclerosis	0	72	100	160/90–275/150 (mean, 220/135)	27	18	9	81	64
Malignant nephrosclerosis	0	54	90	205/120–260/165 (mean, 240/150)	90	72	18	90	54
Healed pyelonephritis	0	54	90	90/60–210/150 (mean, 210/130)	78	54	27	45	9
Chronic pyelonephritis	0	50	100	105/80–270/130 (mean, 140/90)	25	0	0	37	17

manifestations of retinal and vascular changes as well. This so-called "hypertensive neuroretinopathy" is generally agreed to constitute a grave prognostic sign, and by many its presence is considered to merit a diagnosis of malignant hypertension. Although 9 of the 10 cases of malignant nephrosclerosis in which the eyegrounds were examined showed papilledema, it is of great interest that 7 of 9 cases of healed pyelonephritis had similar fundal changes, and they occurred in one or more cases of each of the other groups. Hence, although the pathologic entity, malignant nephrosclerosis, almost invariably presents the clinical picture of malignant hypertension, the converse is not true. Clinical malignant hypertension, as judged especially by retinal changes, not only is produced by malignant nephrosclerosis, but often occurs in healed pyelonephritis and may be found in any of the types of nephritis discussed here.

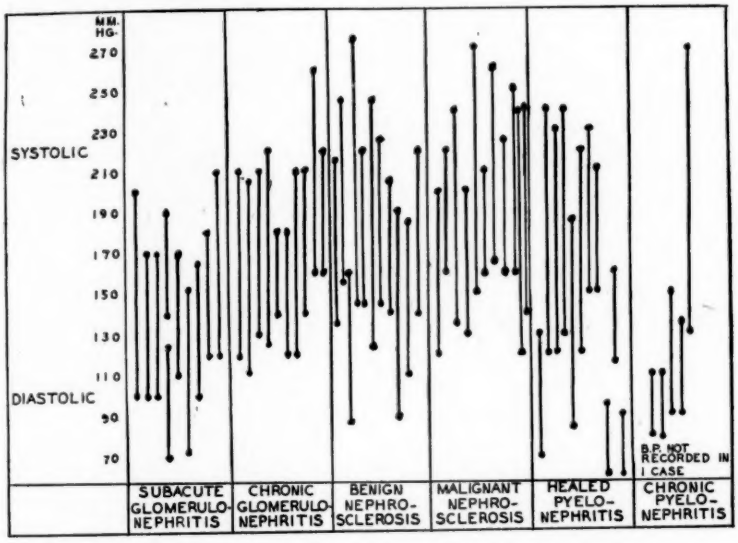

FIGURE 1. *Average Blood-Pressure Readings in Various Types of Chronic Bright's Disease at Time of Last Hospital Entry.*

Urinary Findings

As shown in Tables 2 and 3, no pattern of urinary findings is pathognomonic of any one type of nephritis. However, marked proteinuria, hematuria, pyuria and cylindruria occurred with great regularity in subacute glomerulonephritis and almost as often in chronic glomerulonephritis. Malignant nephrosclerosis presented a picture ranging from an almost normal urine to one resembling that of glomerulonephritis; the same was true of benign nephrosclerosis, although severe changes were uncommon.

Although pyuria was always present in chronic pyelonephritis, this was not true in the healed type, since it was absent in 2 cases and of slight degree in several others. Conversely, marked microscopic pyuria may occur in lesions of other types than pyelonephritis.

Too few tests for bacteriuria and pyelographic examinations were made to merit analysis. Such studies might in some cases have been of diagnostic help, but it should be pointed out that in our experience, as well as that of others, pyelonephritis may exist with normal pyelographic findings and, at least in the healed type, without bacteriuria.

Few patients were followed in this hospital over a long period with careful studies of their urine. However, in those who were so followed it was apparent that in glomerulonephritis gross urinary abnormalities were present early in the course of the disease, often before the development of significant hypertension. The changes persisted, although terminally the albuminuria and abnormalities in the sediment occasionally diminished slightly in amount.

In contrast, patients with nephrosclerosis frequently exhibited comparatively little in the way of urinary abnormalities until late in the disease. The patients with healed pyelonephritis did not follow a consistent pattern. In some of these cases, as in nephrosclerosis, the urine was normal or nearly so for long periods of time, whereas in others persistent or intermittent pyuria occurred and microscopic hematuria was occasionally found.

Leukocyte Count

Leukocytosis of some degree was present in almost all cases at some time.

Nephrotic Stage

By the term "nephrotic stage" is meant the clinical syndrome in which generalized edema, usually marked in degree, dominates the picture. There was no known nephrotic stage in any of the disease groups except those of subacute and chronic glomerulonephritis. In the subacute group it was present in 9 of 10 cases, lasting from a month to a year. In the chronic group it occurred in only 3 of 10 cases.

TABLE 3. *Summary of Urinary Findings at Terminal Hospital Admission.*

Urinary Finding	No. of Cases			Total No. of Cases
	0	+ to +++	++++	
Proteinuria:				
Subacute glomerulonephritis	0	0	10	10
Chronic glomerulonephritis	0	3	7	10
Malignant nephrosclerosis	0	5	6	11
Benign nephrosclerosis	1	10	0	11
Healed pyelonephritis	1	6	4	11
Chronic pyelonephritis	0	3	3	6
	0	+ to +++		
Hematuria (microscopic):				
Subacute glomerulonephritis	0	9		9
Chronic glomerulonephritis	2	4		6
Malignant nephrosclerosis	7	4		11
Benign nephrosclerosis	6	3		9
Healed pyelonephritis	7	3		10
Chronic pyelonephritis	1	5		6
	0	+ to ++++		
Pyuria:				
Subacute glomerulonephritis	0	10		10
Chronic glomerulonephritis	0	9		9
Malignant nephrosclerosis	1	9		10
Benign nephrosclerosis	0	7		7
Healed pyelonephritis	2	8		10
Chronic pyelonephritis	0	6		6
	Granular	Cellular	Hyaline	
Cylindruria:				
Subacute glomerulonephritis	9	5	0	10
Chronic glomerulonephritis	5	2	1	10
Malignant nephrosclerosis	7	1	4	11
Benign nephrosclerosis	4	0	2	11
Healed pyelonephritis	6	0	0	11
Chronic pyelonephritis	1	0	1	6

This type of edema is related to hypoproteinemia and marked proteinuria. Consistent with this is the fact that the plasma protein of 7 of 9 patients with subacute glomerulonephritis was below 5 gm. per 100 cc. during the last part of their stay in the hospital, and in no other group were protein levels below 5 gm. found. The patients with subacute glomerulonephritis either showed nephrotic edema at the time of death or had had it in the recent past. Those with chronic glomerulonephritis had exhibited edema months or years prior to death.

In 2 of the cases of subacute glomerulonephritis with nephrotic edema, the edema cleared in the weeks before death as renal failure advanced; in the other 7, however, it persisted. In 3 of these cases mild heart failure occurred in the late stages of the disease.

Edema that was not clearly cardiac occurred in 2 patients with malignant nephrosclerosis and in 1 with healed pyelonephritis, but this edema was mild and may well have been due to other than renal causes.

Renal Failure (Uremia)

If one takes as a rough measure of uremia the presence of a blood nonprotein nitrogen above 60 mg. per 100 cc., — not due to extrarenal causes, — all the patients in all groups suffered from it during their terminal hospital stays, with the exception of 2 cases of subacute glomerulonephritis and 1 each of malignant nephrosclerosis and healed pyelonephritis (Tables 2 and 4). Even these 4 patients had nonprotein nitrogen levels above 50 mg. at some time during their final stay in the hospital. The degree of nitrogen retention was studied but showed nothing characteristic in the different groups.

In our series the absolute duration of the renal failure frequently could not be told, since many of

TABLE 4. *Cause of Death in Cases of Chronic Bright's Disease.*

Cause of Death	Subacute Glomerulonephritis	Chronic Glomerulonephritis	Benign Decompensated Nephrosclerosis	Malignant Nephrosclerosis	Healed Pyelonephritis	Chronic Pyelonephritis
Uremia	8	3	4	3	7	4
Uremia and contributory heart failure	0	2	2	4	1	1
Uremia and heart failure	0	3	5	2	0	0
Heart failure and contributory uremia	0	1	0	0	1	0
Cerebral accident and uremia	0	1	0	1	1	0
Heart failure and toxemia of pregnancy	1	0	0	0	0	0
Cerebral accident	0	0	0	1	1	0
Nephrosis and bronchopneumonia	1	0	0	0	0	0
Peritonitis and postoperative shock	0	0	0	0	0	1*

*No determination of blood nonprotein nitrogen done.

the cases came under observation only at a time when uremia was already present. However, from the known duration of uremia shown in Figure 2 it can be seen that uremia of relatively long duration is common in glomerulonephritis and benign nephrosclerosis and may occur in pyelonephritis.

Tests designed to show early diminution in renal function, such as concentration tests, phenolsulfonephthalein excretion, clearance tests and so forth, were done too infrequently to be of value in this study.

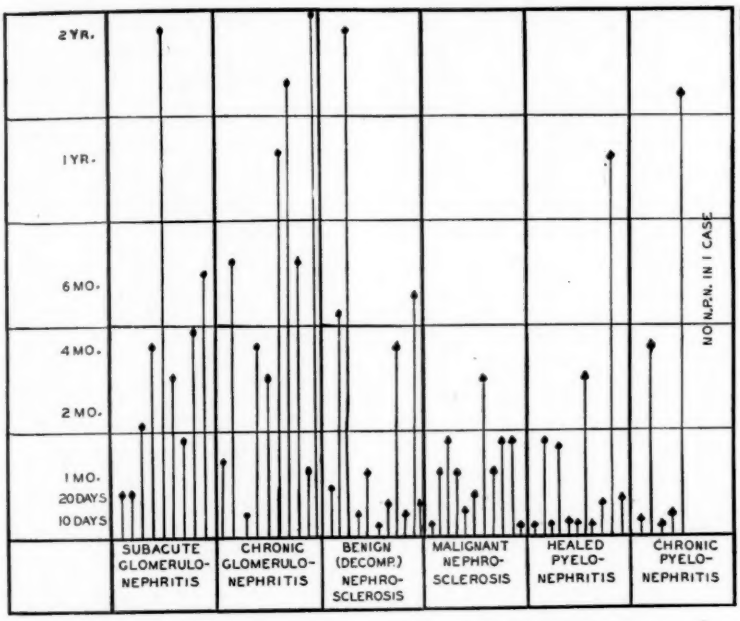

FIGURE 2. *Known Duration of Nitrogen Retention (above 60 mg. per 100 cc.) in Various Types of Chronic Bright's Disease.*

Anemia

In general the anemia was of a normocytic type and tended to be related to the degree and especially the duration of renal failure. In 2 cases anemia of this type had existed for three months before the nitrogen retention exceeded 60 mg. per 100 cc., and in 2 cases nitrogen retention of this amount or more had persisted for twelve and twenty-four months, respectively, before anemia occurred, but in all other cases the known durations of anemia and of nitrogen retention tended to parallel each other, and in every case in which anemia did not occur the known uremia had existed for six weeks or less.

Heart Failure

The importance of heart failure as a primary or contributing cause of death is shown in Tables 3 and 4. It was commonest in patients with decompensated benign nephrosclerosis, where, in spite of the fact that only cases involving death in uremia were chosen, 7 of 11 had significant degrees of heart failure. Moreover, it occurred frequently in chronic glomerulonephritis and malignant nephrosclerosis.

Hypertensive Encephalopathy

Table 2 shows the incidence of this manifestation, which was taken to include episodes of blurred vision, transitory loss of consciousness, aphasia, transient paralysis and so forth. It appeared to be correlated to some extent with the degree of hypertension or of generalized vascular disease or both.

Cerebral Accidents

The occurrence of cerebrovascular accidents is shown in Table 2. In both cases of malignant nephrosclerosis, in 2 cases of healed pyelonephritis and in 1 case of chronic glomerulonephritis the cerebral episodes were the chief immediate cause of death (Table 4).

DISCUSSION

The clinical manifestations in the advanced stages of chronic Bright's disease are not specific for different pathological types. This has been pointed out before by others, but requires re-

emphasis since there still exists confusion in the minds of many. These clinical manifestations are in the main dependent on either failing renal function or arterial hypertension and its sequelae or both. A lesion of any type if sufficiently severe, diffuse and long lasting may so damage the kidney as to cause its function to fail, and when renal failure occurs the clinical picture tends to conform to a certain general pattern regardless of the initiating cause.

Moreover, it is also increasingly evident that many types of renal disease may be accompanied by chronic hypertension, that this hypertension may be of any degree of severity, and that when it is once established the complications that occur are those of chronic hypertension and its associated vascular disease, and are not dependent on the primary causative factor. In certain types of nephritis — for example, glomerulonephritis and pyelonephritis — there is good reason to believe that the renal factor is of primary importance in producing the hypertension. In nephrosclerosis, on the other hand, there is as yet no good evidence that the renal pathologic changes are not secondary to a preceding hypertension of unknown etiology, although once established a vicious circle may be set up, so that the renal ischemia resulting from the nephrosclerosis may aggravate the arterial hypertension, which in turn increases the pathologic change within the kidney.

There are, however, certain features in the life history of the different varieties of chronic nephritis that occur with greater frequency in one type than in another, and there are a few clinical manifestations that are to be found in one type only. Hence the attempt of the clinician to make a diagnosis based on the underlying pathology is not entirely fruitless, since in many cases a proper evaluation of the various clinical factors should lead to the correct diagnosis.

The clinical findings can best be evaluated and understood in the light of the present knowledge of the pathogenesis of the various types of chronic nephritis. Thus, although the fundamental etiology of nephrosclerosis is unknown, it is clear that in the fully developed state there is evidence of widespread vascular disease, and that the malignant type differs from benign nephrosclerosis in the severity of the changes and the rapidity with which they occur. It is obvious, therefore, why nonrenal manifestations, especially in the brain, are commoner in nephrosclerosis, particularly the malignant type, than in the other groups. In malignant nephrosclerosis it is not uncommon for failure of the kidneys, heart and cerebral circulation to occur almost simultaneously. As emphasized by Weiss and Parker,[6] widespread vascular disease is infrequent in patients with hypertension secondary to pyelonephritis.

Several factors combine to produce strain on the heart in chronic nephritis: the height of the blood pressure; the duration of the hypertension; coronary vascular disease; the anemia, which lowers the oxygen-carrying power of the blood and tends to produce an increased cardiac output; and the toxic effect of the uremia on the myocardium. Hence it is not surprising that heart failure occurs so frequently in all groups.

The renal lesion is most obviously present and dominant in glomerulonephritis, and in this group, findings directly related to renal involvement are most constantly present. A striking finding in our series was that the nephrotic syndrome occurred only in glomerulonephritis.

The only variety of Bright's disease that usually runs a characteristic clinical course easily distinguishable from the other types is subacute glomerulonephritis. The onset can most often be definitely dated following an upper respiratory infection, and may be typical of acute nephritis. Occasionally there is a subsequent interval when the patient is free of symptoms, with one or more relapses following further respiratory infections, but frequently the course is progressive from the onset, with nephrotic edema dominating the picture and death ensuing in a few months to a few years. Increasing impairment of renal function takes place, followed by uremia, sometimes hastened by intercurrent infections. The manifestations and complications of hypertension are ordinarily less striking in this type of nephritis than in the others, although even here some degree of heart failure is not infrequent in the late stages.

Whether it is justified on either clinical or pathological grounds to classify subacute separately from chronic glomerulonephritis is open to question. All gradations between the two types exist. The disease is considered subacute when it has progressed so rapidly that death occurs before scarring, and hypertension with its vascular changes takes place to a significant or dominating degree. Conversely, in chronic glomerulonephritis the initial renal lesion is often not so extensive as to produce the nephrotic syndrome or so overwhelming as to result in early death, but does result in renal changes leading to hypertension. There is thus initiated the vicious circle of hypertension and vascular renal change already mentioned. In any case the term "subacute" is an unfortunate one, since this stage of the disease may last for years.

Summary and Conclusions

A clinicopathological study has been made of chronic Bright's disease, comprising (as defined by post-mortem examination of the kidneys) 10 cases of subacute glomerulonephritis, 10 of chronic glomerulonephritis, 11 of decompensated benign nephrosclerosis, 11 of malignant nephrosclerosis, 11 of healed pyelonephritis and 6 of chronic pyelonephritis.

Glomerulonephritis, malignant nephrosclerosis and healed pyelonephritis terminated in youth and early middle age, benign nephrosclerosis occurred after fifty, and chronic pyelonephritis was found at all ages.

An acute onset following respiratory infections usually occurred in subacute glomerulonephritis but was recorded much less often in chronic glomerulonephritis. A history of acute pyelitis was rarely elicited in the pyelonephritic cases.

The known duration of disease was usually relatively short in malignant nephrosclerosis (two years or less, with one exception); in the other conditions the range of duration was much greater.

In malignant nephrosclerosis, terminally a well-marked arterial hypertension was consistently present, and this also usually occurred in benign nephrosclerosis, healed pyelonephritis and chronic glomerulonephritis.

Nine of 10 cases of malignant nephrosclerosis and 7 of 9 cases of healed pyelonephritis showed retinitis with papilledema. This also occurred in 25 to 50 per cent of the cases in the other groups.

There is no pattern of urinary findings pathognomonic of any one type of nephritis. In healed pyelonephritis the urinary findings may be minimal, and pyuria may be absent.

The nephrotic syndrome occurred only in glomerulonephritis.

Renal failure occurred in all cases, although in 2 cases of subacute glomerulonephritis and 1 each of malignant nephrosclerosis and healed pyelonephritis it was minimal. Uremia of relatively long duration is frequent in glomerulonephritis and benign nephrosclerosis and may occur in pyelonephritis. Anemia tended to be related to the degree and especially the duration of renal failure.

Heart failure occurred commonly in all groups and with great frequency in both types of nephrosclerosis. It was often the primary or an important contributory cause of death.

Cerebrovascular symptoms were apparently related to the degree of hypertension or of generalized vascular disease or both, and were commonest in malignant nephrosclerosis.

The clinical manifestations in advanced stages of chronic Bright's disease are not specific for different pathological types. They are, in the main, dependent on failing renal function or on arterial hypertension and its sequelae or both. There are, however, certain features in the life history of the different types of Bright's disease that occur with greater frequency in one type than in another, or rarely are seen only in one. Hence, a clinical diagnosis based on the underlying pathology should be attempted and may be helpful in governing prognosis and treatment.

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FAMILIAL AURICULAR FIBRILLATION*

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AURICULAR fibrillation is one of the commonest disorders of the cardiac mechanism, and its frequent occurrence in patients with otherwise normal hearts is now widely recognized. In spite of this, its familial incidence has been observed but rarely. The first recorded observation of this sort was made by Orgain, Wolff and White[1] in 1936. In 1942, Levy[2] reported the occurrence of paroxysmal auricular fibrillation and flutter without signs of organic cardiac disease in two brothers. The present paper records in detail the findings in three brothers with auricular fibrillation, mentioned briefly in the earlier report,[1] as well as 2 new cases of auricular fibrillation in brothers.

CASE REPORTS

CASE 1. H. K., a 25-year-old real-estate agent, presented himself for examination in 1927 for the purpose of having his heart "straightened out," so that the extra premium he was paying for life insurance might be removed. His mother and father, as well as two brothers (Cases 2 and 3), were alive and well. His mother was said to have had rheumatic fever. There was a possible history of diphtheria in childhood, mild influenza in 1918 and occasional sore throats prior to tonsillectomy in 1921. Frequent nosebleeds had occurred in childhood. Four to five years previously, the patient suffered from back pain, for which no cause could be found.

At birth, the attending physician thought the heart was irregular. From the age of seven through childhood he had always had a grossly irregular pulse. The diagnosis of auricular fibrillation was made for the first time when he was 20 years old, and a course of quinidine therapy at that time failed to abolish the abnormal rhythm. He lived an active, unrestricted life, and had palpitation only when excited. Although he was nervous and had fainted several times, he felt perfectly well and was apparently in excellent health. He smoked twenty cigarettes every day and drank occasionally, sometimes to excess.

Physical examination showed a well-built, healthy-looking young man. The only abnormality was the presence of a grossly irregular heart and a slight, inconstant apical systolic murmur. The apical rate was 80 per minute and was uninfluenced by exercise. The blood pressure was 110/70. The electrocardiogram was normal except for auricular fibrillation. After complete digitalization, quinidine sulfate restored normal rhythm. An electrocardiogram taken within an hour showed a PR interval of 0.16 second and digitalis T waves.

One and a half years later, after a drinking bout, auricular fibrillation recurred. Quinidine alone failed to restore normal rhythm. The patient was therefore digitalized. Quinidine then abolished the abnormal rhythm. He remained well for 2½ years, when another drinking bout was followed by the occurrence of auricular fibrillation. Again digitalis and quinidine restored the normal cardiac mechanism. Another recurrence of auricular fibrillation, without obvious cause, took place 1½ years later. Although digitalis and quinidine again restored normal rhythm, the rhythm became irregular within 2 months. After a short trial of quinidine therapy by the family physician without success, further treatment was refused. Up to the present time (February, 1943), the patient's health has remained excellent in spite of persistent auricular fibrillation. Digitalis has not been required.

CASE 2. V. K., a 31-year-old businessman, presented himself for examination in March, 1928, for treatment of a cardiac condition that he believed similar to that of his brother (Case 1). He had had measles, diphtheria, pertussis, mumps and tonsillitis in childhood. At the age of 8, he had pains in the legs, but was not disabled. The tonsils and adenoids were removed when he was 13 years old. In 1917, he had influenzal pneumonia and was in bed for 2 weeks. He smoked thirty cigarettes daily, but used very little alcohol, coffee or tea. As far back as he could remember, he had been very nervous and had had a quick temper. During the last 4 years his responsibilities had greatly increased, and he had had several fainting spells during this period.

The heart had been irregular since early childhood, but a diagnosis of auricular fibrillation had been made for the first time 7 months before the present examination. The patient played tennis and baseball and was very active generally. His only complaint was palpitation under great excitement.

Physical examination showed a well-developed, fairly well-nourished man. The heart rhythm was absolutely irregular at a rate of 76 per minute, which corresponded with the pulse rate. The sounds were of good quality and there were no murmurs. The blood pressure was 108/80. Electrocardiographic tracings showed auricular fibrillation with a ventricular rate of 70. There were no other abnormalities. After complete digitalization, quinidine caused a reversion to normal rhythm. Electrocardiograms then showed a PR interval of 0.20 second and digitalis T waves. Examination of the heart revealed no abnormalities except for a systolic murmur that was audible at the apex and pulmonic area but disappeared completely on full inspiration. Two days later the PR interval was 0.16 second.

When the patient was last seen, 20 months after the first examination, normal rhythm was still maintained. He had been living his usual active life, smoking as much as ever and occasionally drinking, without any harmful effects.

CASE 3. M. K., a 24-year-old law student, was first seen in June, 1928, at the request of his two brothers (Cases 1 and 2). During childhood he had had measles, an occasional cold and rarely a sore throat. For several years, when tired, he had had generalized, steady, dull pains in

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the legs. At the age of 9, herniotomy and tonsillectomy were performed, and at the age of 15 the appendix was removed. The patient smoked twenty to twenty-five cigarettes every day, and drank two or three cups of coffee and one cup of tea daily and alcohol irregularly.

At the age of 14, he was told that his heart was irregular and was advised to avoid strenuous exertion. Nevertheless, he played tennis, baseball, football and hockey, and could swim 3 miles without untoward symptoms. He had palpitation only when excited. Nervousness was always marked, and fainting or dizziness occasionally occurred.

Physical examination revealed a tall, fairly well-nourished young man. There were no abnormalities except for an absolutely irregular cardiac rhythm. The apex and pulse rates were 80 per minute. The blood pressure was 118/80. Electrocardiograms were normal except for auricular fibrillation; the ventricular rate was 70. After complete digitalization, quinidine restored normal rhythm. Electrocardiograms taken immediately after the change in rhythm showed a PR interval of 0.20 second and digitalis T waves.

The patient was seen for the last time 2 months after the first examination. Normal rhythm was still maintained.

Case 4. S. O. S., a 35-year-old physical director, was first seen in April, 1928. The chief complaint was palpitation of 10 years' duration. The past history was negative except for Neisserian infection 17 years previously, mild influenza in 1918 and psoriasis 1 year previously.

His general health had always been excellent except for attacks of palpitation, which occurred about once a week and lasted half an hour and were apparently related to excitement, exertion or the drinking of whiskey. During the attacks, he was conscious of rapid and irregular heart action. Although he felt weak, he continued whatever activity he was engaged in. Less frequent attacks of a different type of palpitation occurred in which the heart beat much more rapidly and was regular except for occasional intermittence. They were stopped by bending forward. The patient's activities consisted of wrestling, boxing, swimming and road work; he could run 10 miles without untoward symptoms. He was nervous and introspective.

Physical examination disclosed a well-developed and well-nourished, muscular, healthy athlete. The heart was normal, but the first apical sound was reduplicated. The blood pressure was 104/70. The tip of the spleen was just palpable. Roentgenographic measurements of the heart were within normal limits. The blood Wassermann reaction was negative. Electrocardiograms were obtained during paroxysms of auricular fibrillation as well as during normal rhythm.*

Seven years later (1935), after untreated persistent auricular fibrillation for 6 months, the patient was examined at another clinic,[4] where congestive failure and moderate cardiac enlargement were found. Following digitalization, quinidine restored normal rhythm. Improvement was striking, and for the next 5 years he was able to carry on well. There was an occasional paroxysm of auricular fibrillation. In 1939, the transverse diameter of the heart was 14.8 cm., compared to 14.1 cm. in 1928.

Case 5. S. S., the 25-year-old brother of the patient in Case 4, entered the Beth Israel Hospital in March, 1931, complaining of attacks of palpitation of 2 years' duration. In childhood he had had diphtheria, measles, scarlet fever and frequent sore throats. He drank whiskey and beer occasionally and two or three cups of coffee daily; he did not use tobacco.

During the last 2 years he had had several attacks of palpitation lasting as long as 36 hours. Ten months before admission, after exercising in a gymnasium, he had an attack accompanied by constricting precordial pain. Examination showed auricular fibrillation and spontaneous pneumothorax (x-ray). Following this he had palpitation and dyspnea, especially at night, but continued working strenuously as a warehouseman and played basketball and other games. He was nervous and introspective.

Examination revealed no abnormal findings except auricular fibrillation, with an apical rate of 90 per minute. The blood pressure was 122/80. The basal metabolic rate was +10 per cent. Electrocardiograms showed a tendency to right-axis deviation, auricular fibrillation with a ventricular rate of 100 and normal T waves and RST segments. After reversion to sinus rhythm, normal P waves and PR intervals were present. A roentgenogram of the chest revealed slight scarring of the left apex and emphysema. After complete digitalization, quinidine restored normal rhythm.

During the succeeding 8 years, paroxysms of auricular fibrillation have recurred occasionally, but the patient's general health has remained good. At present, there is no evidence of structural heart disease.[5]

Discussion

The great frequency and ease of recognition of auricular fibrillation warrant the conclusion that the familial occurrence of this arrhythmia is rare. Indeed, the two sets of brothers here reported are unique in medical literature; in the cases reported by Levy,[2] one brother had auricular fibrillation, the other auricular flutter. This is in marked contrast to other common disorders of the heart such as rheumatic, hypertensive and coronary heart disease, in which it is not unusual for several cases to occur in a single family.

There are several noteworthy features in the first set of brothers (Cases 1, 2 and 3). One of them had frequent nosebleeds, the other two growing pains in childhood. During the fetal life of M. K. (Case 3), his mother is said to have had rheumatic fever. All three brothers had permanent auricular fibrillation, in contrast to paroxysmal fibrillation in the remaining cases in a series with normal hearts previously reported.[1] An arrhythmia was constantly present years before a diagnosis of auricular fibrillation was made, suggesting that an abnormal mechanism was present at birth or developed early in life. Congenital auricular fibrillation is suggested, particularly in Case 1. The three brothers lived normal, unrestricted lives, and two of them engaged in strenuous sports without difficulty of any sort. Although the ar-

*A more complete description of these electrocardiographic tracings may be found in a previous publication by Wolff, Parkinson and White.[3]

rhythmia was untreated, the ventricular rates were slow, even after exercise. Auriculoventricular conduction time, measured in each case immediately on resumption of sinus rhythm, was normal. It was thought that an unusually rapid auricular rate (circus movement) might be responsible for the slow ventricular rate, since it was possible to count 800 oscillations to the minute in the limb leads as well as in chest (CB) leads (Case 3). Notching of the auricular deflections, however, could have accounted for the apparently rapid rate. A more likely explanation for the slow ventricular rate was furnished by the evidence of strongly preponderant vagal tone, which also may have been a factor in the production of auricular fibrillation.[6–10] With normal rhythm, each of the brothers had a very slow and irregular heart (sinus arrhythmia). Nervousness, low blood pressure, dizziness and fainting spells were also present. There was no evidence of thyrotoxicosis.

The benign nature of auricular fibrillation, provided that the ventricular rate is controlled and embolism does not occur, is illustrated by these cases. In spite of the abnormal rhythm of many years' duration, completely unrestricted activity was possible, even without the use of digitalis or other cardiac drugs. The heart size remained normal, and it was impossible to demonstrate any structural abnormality whatsoever.

Case 4 is of historical interest, being the first in which the combination of short PR interval, changes in QRS complexes resembling bundle-branch block and paroxysmal tachycardia was recognized as a distinct clinical entity.[3] This mechanism was not demonstrable in the patient's brother (Case 5), but in other respects they were much alike. There was no evidence of thyrotoxicosis.

The value of the combined administration of digitalis and quinidine for abolishing auricular fibrillation, especially when quinidine alone is ineffective, is again demonstrated by these cases.[11]

Summary

Permanent auricular fibrillation in three brothers and paroxysmal fibrillation in two brothers, with otherwise normal hearts, have been reported. Familial auricular fibrillation is apparently rare, in contrast to certain other cardiac disorders that commonly occur in several members of a single family.

There is evidence of increased vagal tone in these cases, suggesting a probable etiologic factor in the production of auricular fibrillation in certain cases.

Auricular fibrillation, even when untreated and of many years' duration, is entirely benign, provided that the ventricular rate is slow and embolism does not occur. Under these conditions, auricular fibrillation does not cause cardiac enlargement.

The combined administration of digitalis and quinidine for abolishing auricular fibrillation was in these cases superior to the use of quinidine alone.

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ACUTE PNEUMONITIS AND PERICARDITIS*

Report of a Case

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LIEUTENANT J. WILLIAM QUINLAN (MC), U.S.N.R.

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BECAUSE of the widespread interest in the prevalent pulmonary infection known variously as pneumonitis, virus pneumonia or simply atypical pneumonia, the following clinical history is presented. We were particularly interested in interpreting the bizarre changes in the electrocardiograms of this patient as correlated with the clinical and x-ray findings. We have subsequently observed the same cardiographic changes, to a lesser degree, in certain other patients suffering from this condition, particularly since we now take routine tracings on all patients with respiratory infections who have temperatures of 100°F. or over. In 11 out of 100 cases observed, an elevation of the ST segment of 2 mm. above the isoelectric line (generally in Lead 4) was noted. In 5 additional cases there was inversion of the T wave in Lead 4. On recovery, all the variations returned to normal.

CASE REPORT

C. J., a 36-year-old man, was admitted to the Medical Service of the United States Naval Hospital at Newport, Rhode Island, on July 8, 1942, complaining of pain in the interscapular region of 1 week's duration and of nonproductive cough. The backache was sharp in character and grew worse on movement, breathing or coughing. There had been no chills. He had suffered from an upper respiratory infection (sore throat, fever and cough) 3 weeks previously. This had cleared except for a residual cough.

The past history revealed the occurrence of pleurisy at the age of 11. The family history was noncontributory.

Physical examination disclosed an acutely ill man, slightly cyanotic and somewhat dyspneic. Dullness was noted over the lower lobe of the right lung posteriorly, below the angle of the scapula. Slightly increased breath and voice sounds and coarse rales were heard. The left lung showed dullness at the base, with scattered rales. Percussion of the heart revealed possible enlargement. No murmurs or friction rub was heard. The blood pressure was 110/60. The temperature was 99.4°F., and the pulse 83.

The white-cell count was 10,500, with 68 per cent neutrophils and 23 per cent lymphocytes. The sedimentation rate was increased. The antistreptolysin titer was normal. The sputum contained some gram-positive diplococci, which could not be typed.

X-ray examination revealed an infiltration of both lower lung fields, especially the left, and enlargement of the cardiac silhouette. An electrocardiogram presented an inverted T wave in Lead 1 and an elevated ST segment in Leads 2, 3 and 4 (Fig. 1). On July 11, x-ray films showed recession of the process in the lower left chest but increased density in the lower part of the right lower lobe. On July 15, the T waves were inverted in Leads 1, 2 and 4, with coving (Fig. 2), and x-ray examination showed clearing in the right lower lobe but involvement of the right middle lobe. On July 20 (about the 20th day after onset), the T waves were upright in all leads and the electrocardiogram had returned to normal (Fig. 3).

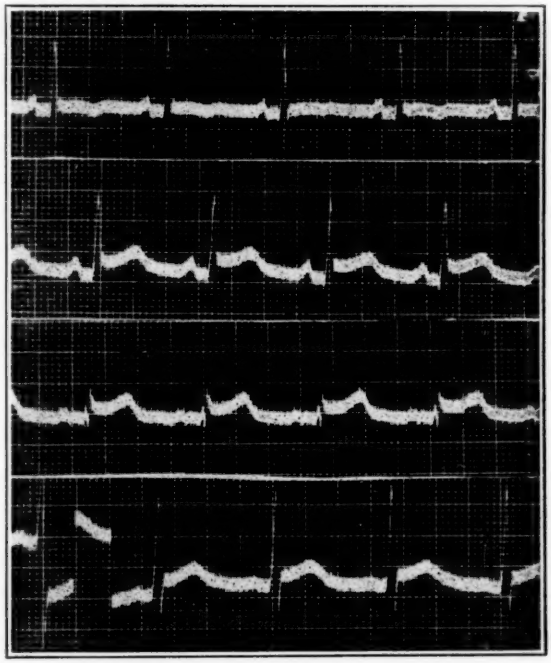

FIGURE 1. *Electrocardiogram Taken on July 8.*

The following day, the patient suffered a recurrence of pain between the shoulderblades and in the epigastrium. X-ray examination demonstrated an infiltrating lesion in the upper portion of the right lower lobe. The cardiac silhouette, however, had returned to normal size. An electrocardiogram on the following day revealed inverted T waves in Leads 1, 2 and 3 (Fig. 4). The next x-ray examination, performed on July 28, again showed clearing in the right lower lobe but also demonstrated a new le-

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sion in the right middle lobe. Clinical findings, x-ray evidence and electrocardiographic changes remained the same until August 4, when the chest film showed considerable improvement. The T waves were still inverted in Leads 1 and 3, but by August 12 the tracing had returned to normal and remained so. On that date x-ray examination also showed complete resolution of the pneumonic processes. Sulfonamide therapy was of no avail during either the initial stage of the illness or the relapse.

At the time of first examination the problem appeared to lie in ruling out myocardial infarction. We finally decided for the reasons given below that not coronary occlusion but pericarditis was producing the alterations in the electrocar-

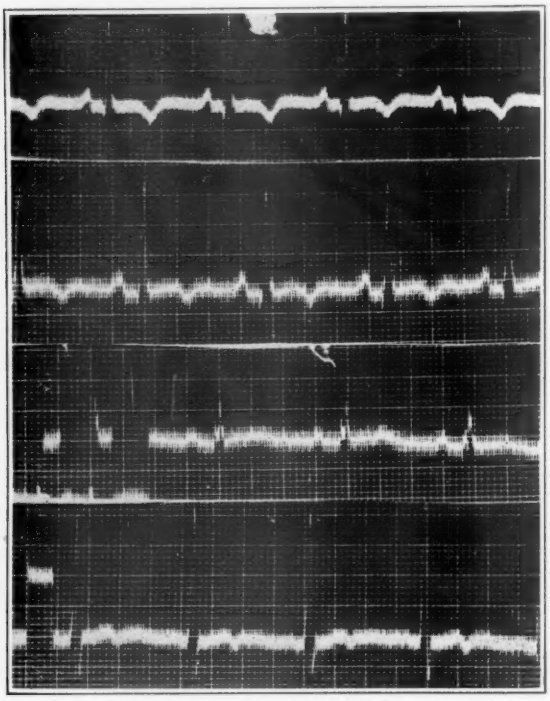

FIGURE 2. *Electrocardiogram Taken on July 15.*

diographic pattern. Early in the differential study dissecting aneurysm was considered, because of the location of the pain, but this possibility was dismissed for want of evidence and because of the manifestations of pulmonary and cardiac changes. Acute mediastinitis was discussed, but Commander E. F. Merrill, roentgenologist at the hospital, did not think that the x-ray evidence supported this possibility. Fiedler's interstitial myocarditis was given but slight consideration. Although this condition may produce somewhat similar electrocardiographic changes and initially may resemble the clinical picture as presented, the return of the heart to normal size and the complete recovery of the patient eliminated this possibility.

The next problem was concerned with the pulmonary changes. It was thought that the rapid-

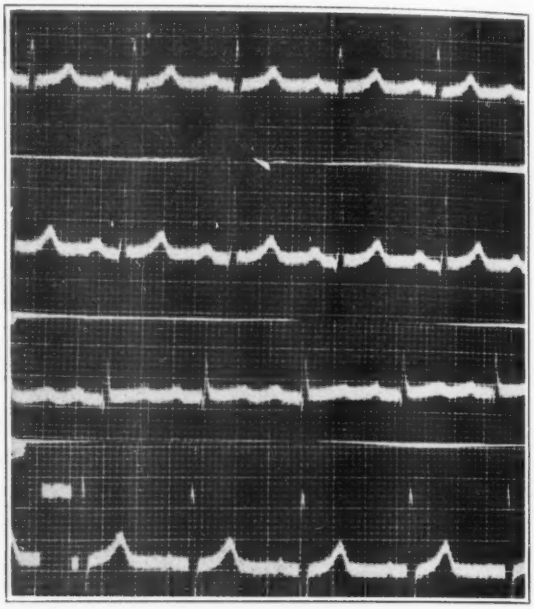

FIGURE 3. *Electrocardiogram Taken on July 20.*

ity of clearing of the pulmonary fields and the lack of residual alterations eliminated multiple pulmonary infarctions as the source of the lesions. Rheu-

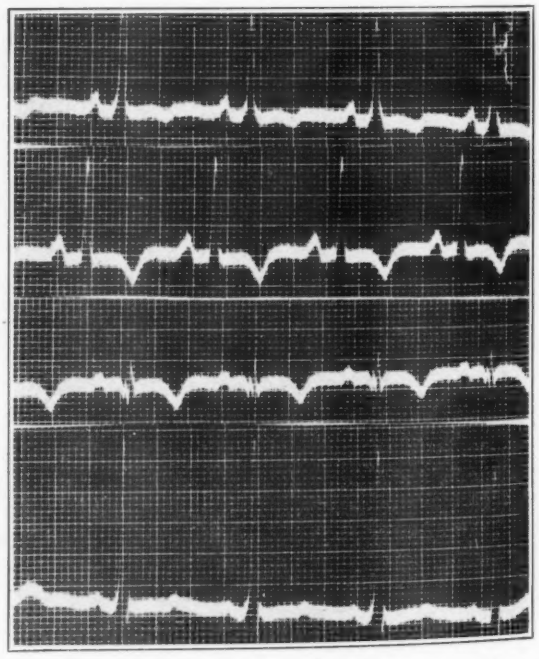

FIGURE 4. *Electrocardiogram Taken on July 22.*

matic fever with rheumatic pulmonary changes and pericarditis might produce the picture de-

scribed. However, at no time did the patient manifest joint involvement and he never exhibited any signs of congestive failure, a finding that is frequently observed with so-called "rheumatic pneumonitis." It is true that the sedimentation rate was increased, but this would be expected in the presence of any acute pulmonary infection. The antistreptolysin titer was normal, however, and we have found this to be uniformly elevated during active rheumatic fever, especially during the first attack. Following the subsidence of the pericarditis no other evidence of acute rheumatic fever with rheumatic heart disease was found. On the basis of these facts we eliminated this entity in favor of one that consistently manifested x-ray changes similar to those described in this case. In addition, subsequent study produced similar though less marked cardiographic changes in about 15 per cent of the patients with these x-ray changes.

Discussion

This patient displayed five distinct areas of pneumonia during the course of his illness, and it will be noted on following the clinical progress that the variations from and return to normal in the electrocardiograms corresponded closely to the pulmonary changes. These variations consisted in elevation of the ST segment and T wave inversion, frequently with coving. The alterations were in the same direction with regard to the base line in various leads in contrast to the changes in myocardial infarction, which are reciprocal; that is, in infarction due to acute anterior coronary occlusion the ST segments may be elevated in Leads 1, 2 and 4 but are depressed in Lead 3. In addition, no Q wave was noted and there was no disappearance of the R wave in Lead 4, as in anterior infarction. In posterior infarction the ST segment is elevated in Leads 2 and 3 but not in Lead 1, where a depression of this segment may be found. The absence of a prominent Q wave in Leads 2 and 3 also helped to differentiate this condition and posterior infarction. Finally, the pattern changed too rapidly and returned to normal too quickly to correspond with that due to infarction.

The changes were in accord with those found in acute pericarditis. They have been described by many investigators and are believed to be due, not to tamponade of the heart, but to acute subepicardial myocarditis. They are characteristically evanescent and may last only a few days, since the changes are not due to the death of the myocardial tissue but to inflammation. It should be stressed at this point that at no time were any physical signs of pericarditis evidenced — a strong recommendation for the use of the electrocardiogram in similar respiratory infections. The literature shows that the use of Lead 4*R* is preferable to that of Lead 4*F* when this condition is suspected, although we used Lead 4*F* in this study.

One other state should be mentioned as a possible causative factor in the production of the abnormalities, particularly the less marked ones, observed in the tracings of our series. This is hyperventilation, which is known to produce transient electrocardiographic changes. We do not believe that the marked changes produced in the case reported can be accounted for by this phenomenon, but have not investigated it in the other cases with minor changes.

There are three electrocardiographic patterns to be kept in mind as being important from the point of view of differential diagnosis. First of all, a patient who has had a previous pattern of myocardial strain with a superimposed coronary thrombosis may show bizarre tracings similar to those described in this case. Secondly, one must take care to exclude an infarct complicated by bundle-branch block. Thirdly, one must rule out a combined anterior and posterior infarction. The absence of a Q pattern aids in this regard, and in addition the study of serial tracings for evidence of a changing pattern as well as observation of the time interval before the pattern returns to normal, is all important.

Summary and Conclusions

A case of acute pneumonitis with bizarre electrocardiographic findings, presumably due to acute pericarditis, is reported.

It seems advisable to take electrocardiograms in severe cases of acute atypical pulmonary infection. In this way, acute pericarditis may be diagnosed in the absence of physical signs or before the latter appear; and the tracing may aid in accounting for prolongation of illness or unexplained symptoms and signs. Secondly, one should beware of diagnosing coronary occlusion too readily. Serial tracings should be made, and alterations in pattern should be observed, as well as the time interval, before the return to normal occurs.

MEDICAL PROGRESS

BRIGHT'S DISEASES (Concluded)*

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BOSTON

Intercapillary Glomerulosclerosis

THE description by Kimmelstiel and Wilson[51] in 1936 of a severe nephrotic syndrome associated with hypertension and uremia, complicating the course of diabetes mellitus and apparently attributable to a sclerotic lesion between the capillaries of the glomerular tuft that they called "intercapillary glomerulosclerosis," has resulted in a reconsideration of pathologic material in many laboratories and in the clinical segregation of such cases in many diabetic clinics where previously they had been overlooked. This movement has continued during the past year with the appearance of case reports and reviews of necropsy material. Horn and Smetana[52] at Columbia University re-examined diabetic and arterial nephrosclerotic autopsy material and found typical lesions of intercapillary glomerulosclerosis in 22.9 per cent of the diabetic and 25.4 per cent of the nephrosclerotic kidneys, figures that are in striking contrast to those of Siegal and Allen[53] of 33.3 per cent and 1.0 per cent, respectively. The lesions were always associated with arteriosclerosis, and it is noteworthy that the severer lesions were always associated with diabetes mellitus. Bell[54] in Minneapolis has reviewed the kidneys of 460 persons with diabetes, finding hypertension more frequent among them than in the population at large, and finding intercapillary glomerulosclerosis in 20.5 per cent of the diabetic patients. Hyaline masses between the glomerular capillaries, apparently attributable to splitting and thickening of the basement membrane, along with hyalinization of the afferent and efferent arterioles, were the outstanding pathological findings. Horn and Smetana, as well as Bell, stress the nonspecificity of the lesions, which apparently cannot be made the basis of a pathological diagnosis of diabetes mellitus.

Amyloid Nephrosis

During recent years Hass[55–57] at Cornell has conducted a study of the nature of the substance deposited throughout the body in amyloid disease. He has succeeded in separating two protein fractions and a sulfate-bearing polysaccharide from amyloid found in the liver, spleen and other organs. Amyloid from all these sites has common chemical and tinctorial features, although three distinct types of amyloid are identifiable. All are protein-protein complexes and Hass subscribes to the view that all are derived from the deposit and alteration of antibody-antigen combinations. This view is widely held because amyloid deposits appear almost always in conditions where the immune mechanisms have been exposed to prolonged stimulation, as in chronic pyogenic or tuberculous infections. They are easily produced in animals by pyogenic sepsis, especially on the basis of invasion by staphylococci, and by toxins, especially diphtheria toxin when used for the production of immune serum. The appearance of amyloid in such conditions as chronic diffuse glomerulonephritis and multiple myeloma seems to weaken this explanation, but in the first, long-standing occult infections may be at fault, and in the latter the hyperglobulinemia may indicate some connection with the immune mechanisms. The polysaccharide recently isolated by Hass cannot be distinguished chemically from chondroitin-sulfuric acid found in cartilage or from heparin. This gross chemical resemblance to heparin is of interest from the standpoint of pathology, for the lesions are almost invariably found beneath the endothelium of vessel walls. The fact that in vitro production of amyloid with antigen and antibody is not possible is no deterrent to acceptance of the theory, for, as Hass has pointed out, the formation of amyloid is slow and time consuming. Since Congo red, not a unique substance, can easily change the character of amyloid, Hass concludes that many other substances with similar properties are present in the blood and alter the antigen-antibody complex in vivo in a manner that cannot be duplicated in vitro. However, this explanation fails to throw light on the mechanism of the ready and rapid removal of the substance following elimination of the causative focus of infection in many cases. In addition, Snapper[6] notes the extremely low incidence of amyloidosis in China, where 1.3 per cent of the cases of chronic

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tuberculosis are complicated by the disorder in contrast to varying estimates of 22 to 25 per cent in this country.[58, 59] Snapper stresses the apparent importance of a milk-free and casein-free diet in determining the low incidence of amyloid disease in northern China.

Considerable interest has been shown during the past year in the refinement and quantitation of the Congo red test. Harmon and Kernwein[60] suggest the use of 4 mg. per kilogram of body weight, taking blood samples at the usual four-minute and sixty-minute intervals after injection, but Taran and Eckstein,[59] at the Sea View Hospital, Staten Island, New York, point out that Congo red may be removed so rapidly following administration that a sample taken four minutes later will give a falsely low standard, and they suggest shortening this interval to two minutes.

Benign Proteinuria

The appearance of protein in the urine is usually evidence of an underlying renal disorder of a serious character and may include any of the Bright's diseases. However, cases of proteinuria in the absence of demonstrable renal disease include benign albuminuria, orthostatic albuminuria and the larval nephroses, and may be considered arbitrarily as nephroses. The importance of orthostatic albuminuria today in its relation to military medicine has recently been emphasized by Young and his associates,[61] who report 4 cases of men rejected for military service by medical examining boards because of persistent albuminuria. Extensive studies revealed no renal disease, and it was found that the albuminuria appeared only in the erect posture. These men were then accepted for service. Young emphasizes the benignity of the condition and reviews the cases seen at the Johns Hopkins Hospital. In 67 cases, 4 (6 per cent) proved on follow-up to have chronic nephritis. This incidence, however, is high enough to warrant close follow-ups in all cases and should indicate a somewhat less optimistic outlook, although, of course, coincidence cannot be ruled out as a factor in this small series.

Transient proteinuria (larval nephrosis) frequently appears in the course of acute infectious diseases and febrile states. The usual pathological findings include cloudy swelling of the tubular cells and hyaline-droplet degeneration. Kannerstein[62] reviewed the renal lesions found at death in the midst of various acute infectious diseases and found tubular changes most marked in diphtheria, where epithelial necrosis appeared in 16 per cent of cases. Interstitial infiltration appeared in 48 per cent of cases of diphtheria and in 77 per cent of cases of scarlet fever, representing an inflammatory reaction or nephritis that would have been impossible to diagnose clinically.

Therapy of Nephrotic Edema

In most of the nephroses mentioned thus far the management of edema is the outstanding therapeutic problem. Rational therapy must be directed at replacing the lost intravascular protein or at furnishing a substitute with similar properties in order to re-establish normal osmotic relations. To this end, extensive therapeutic programs with the use of transfusions of plasma and serum or concentrates of plasma and serum have been conducted. In many respects this approach has proved disappointing, as is exemplified by the studies in England of Brown, Gray and Mollison[63] appearing during the past year. These workers found that concentrated serum and plasma transfusions were not followed in most cases by increased plasma protein and in fact seemed as likely to be followed by adverse effects as by good effects, results confirming several earlier studies in this country. The use of acacia as a substitute for the lost plasma proteins has found support in the United States, particularly at the Mayo Clinic, where acacia has been given an extensive therapeutic trial. During the past year Lehnhoff and Binger[64] have added 12 more cases of nephrosis treated effectively with acacia to the series already reported from the Mayo Clinic. They find the substance efficacious in relieving the edema of nephrosis and believe that it is safe. However, there is experimental proof that acacia is stored in the liver, to remain there for long periods of time.[65] Heckel, Erickson, Yuile and Knutti[66] showed a reduction in plasma proteins after administration of acacia that could not be entirely accounted for by the increase in plasma volume, apparently indicating liver damage with impaired hepatic regeneration of protein. Farr[49] thinks that the use of acacia is not justifiable since other substances (concentrated human plasma and serum) are available that behave in exactly the same manner and are not dangerous. Obviously, every effort must be made to build up the plasma protein by increasing protein intake. In addition, of course, sodium deprivation is mandatory in preventing to some extent further accumulation of edema fluid.

The diuretics seem to be useful in controlling the edema in many nephrotic patients. Ammonium chloride and the potassium salts are in wide use. Farr[49] recommends urea in doses of 45 to 60 gm. daily because it is effective and seems to be harmless. The mercurial diuretics have not been proved detrimental to the kidney and are

very effective in establishing diuresis. However, the dangers of their use have received much attention during the past year, and editorial warnings have been sounded in the *Journal of the American Medical Association*[67] and in the *Lancet*.[68] These warnings have been addressed to the profession because of the appearance of case reports of sudden death following the administration of mercurial diuretics. DeGraff and Nadler[69] point out that the usual type of toxic response is attributable to the dehydrating action with chloride loss, resulting in a shock-like state. However, by far the most dangerous type is apparently attributable to ventricular fibrillation due to the direct action of mercury on the heart. In all, some 26 fatal cases have been reported, a number that is infinitesimal in comparison with the millions of injections that have been given.

Mercurial Nephrosis

Mercury produces a specific lesion in the renal tubules characterized by necrobiosis, necrosis with sloughing of the epithelial cells into the lumen of the tubule, collapse and rupture of the tubules, and frequently calcification of the necrotic lesions. The lesion is typical in many respects of those seen in the second group of nephroses described above, the necrotizing nephroses. Mercury appears to exert its main effect on the midportion of the proximal tubular segment, rarely with injury to portions of the distal segment and thin segment.[70] The finding of Holman and Donnelly[71] that hypoproteinemia appears to protect the kidney in dogs may explain the infrequent occurrence of renal damage in nephrotic patients treated extensively with mercurial diuretics.

Sulfonamide Nephrosis

Like mercury, the sulfonamides have proved dangerously nephrotoxic. Numerous reports of cases of renal damage during the course of sulfonamide therapy have continued to appear in the literature during the past year. The renal damage has been attributed to the blocking effect of crystals of the free and acetylated drug. This explanation has much to recommend it in the majority of reported cases, for dilatation of the tubules and the malpighian corpuscles anterior to the blocking crystals is frequently seen. In addition, tubular necroses are often observed, and lesions similar to those seen in the crush syndrome have been reported on several occasions. In these cases a hemolytic anemia due to the drug appears to be the most important underlying factor.[72] It is worth remarking that these drugs are relatively safe in the presence of uremia resulting from intrinsic renal disease. Fishberg,[73] for example, describes the successful use of sulfonamide in the treatment of lobar pneumonia appearing in the course of chronic pyelonephritis associated with renal insufficiency and azotemia. This may be ascribed to the low specific gravity of the urine and to the fact that the kidney does not concentrate the drug within the tubular urine at dangerous levels. Small doses of the drug, however, are required to maintain high blood levels in these patients. It is interesting that the sulfonamides appear to become more soluble as urinary concentration increases, owing to the fact that high concentrations of urea render the drugs more soluble.[74] This finding may have therapeutic bearing in supporting the use of urea during the administration of the drug for its action of inducing diuresis and increasing sulfonamide solubility, as well as for whatever bacteriostatic effect it may have. It cannot be emphasized too frequently that adequate hydration and alkalinization are of paramount importance in preventing renal damage by the sulfonamides.

The Crush Syndrome and Related Conditions

During the past year the so-called "crush syndrome" has continued to excite considerable interest[75] and has stimulated numerous efforts to solve its etiology and pathologic physiology. It is becoming increasingly apparent that an important group of renal disorders, nephrotic in type, is achieving homogeneity as a result of these studies. These nephroses include the renal lesions seen following intravascular hemolysis during malaria (blackwater fever) or after the administration of incompatible blood and those seen during myohemoglobinemia and hemolytic anemia due to sulfonamide, as well as those of the crush syndrome. In all these conditions there are numerous casts in the urine, the collecting ducts and the distal tubules, along with necrotic changes in the tubular cells. In all of them the *sine qua non* in the cycle of events leading to uremia seems to be the extracellular appearance of hemoglobin or other heme-bearing pigment in the circulating blood.

Bywaters and his colleagues[76–78] have reported cases of renal insufficiency following crushing injuries seen during the heavy bombing of London in the fall of 1940 as examples of a new syndrome, for they were unaware of similar cases reported in the German literature following World War I. These patients had usually been pinned by the extremities beneath heavy beams or other débris for several hours. Following release they usually

appeared well save for complaints referable to fractures, lacerations and other injuries. The compressed limb was pale, cold and pulseless, with evidence of some motor and sensory loss. Following rescue, tense swelling of the limb appeared and shock became evident with pallor, sweating, hemoconcentration and finally marked hypotension. (Duncan and Blalock[79] have shown experimentally that the shock is attributable to plasma loss into the tissue at the site of compression where capillary walls are damaged.) The swelling of the limb continued, but shock responded well in most cases to the intravenous administration of fluids and blood. Following recovery from shock the patients seemed well, but the urine was found to appear bloody, to contain albumin, creatine and pigmented granular casts, and to be highly acid. During the next few days the urinary output was as a rule very scanty, but the pigment usually disappeared after the second day. Despite the oliguria, the urine remained dilute. Often the condition of the limb aroused concern, and occasionally amputation in the presence of gangrene was performed. During the first week the blood pressure gradually rose to hypertensive levels, vomiting became a prominent feature, and the blood urea, phosphate and potassium levels gradually rose whereas the carbon dioxide combining power fell. At about the end of the first week, a critical diuresis followed by complete recovery occurred or, more frequently, urine flow ceased altogether and the patient died suddenly after two or three more days in uremia. At autopsy the kidneys were found to be engorged and swollen, with striking changes in the distal segment of the renal tubules ranging from cloudy degeneration to frank necrosis. The distal tubules and collecting ducts were jammed with brown granular casts, which were occasionally extruded into the interstitial tissue through the necrotic tubular wall. The muscular tissue at the site of injury was usually also necrotic and markedly pale. Bywaters[80] has emphasized the importance of the condition in modern warfare, since the bombing of urban centers is peculiarly adapted to the production of crushing injuries caused by the collapse of shelters, dwellings or other heavy construction. In an air raid as many as 5 per cent of the casualties may be of this type. More than 70 cases had been reported to the Medical Research Council in England by December, 1942.

When first observed, these cases were thought to be examples of transfusion reactions, but it soon became apparent that the syndrome was seen when transfusions had not been administered and that it appeared only in patients with a history of compression injury. However, Bywaters and his colleagues[81] were struck by the evidence of muscular damage, — namely, the muscular pallor and the creatinuria, — and they believed that a toxic substance, probably myohemoglobin, was released from the muscle. This hypothesis found support in the identification of the pigment in the urine.[82] Bywaters[80] next attempted the experimental production of the renal lesion, and claimed success in producing it in the acidotic rabbit following the intravenous injection of myohemoglobin. However, Bing[83] was unable to confirm Bywaters's results, since in his experiments myohemoglobin proved harmless in the acidified dog. He suggested that Bywaters's effects might be attributable to the use of foreign protein, since the myohemoglobin used by Bywaters was obtained from some species other than the rabbit, which has no myohemoglobin in its muscular tissue.

Myohemoglobinuria occurs in man, however, under other circumstances, and there it is associated with renal insufficiency, a fact further bolstering Bywaters's hypothesis. Bywaters and Dible[84] have reported during recent months the eighth case of paroxysmal myohemoglobinuria to have appeared in man. This condition is seen as a rule in horses, where it is a serious complication of sudden exercise after rest or after heavy feeding and is apparently due to muscular loss of myohemoglobin. The affected muscles become stiff and paralyzed, and death occurs in uremia, in 20 to 70 per cent of cases with evidence of sepsis at the end of the first week. Lesions in the kidney resemble those of the crush syndrome.

On the other hand, renal disorders are known that resemble the crush syndrome in every respect but that do not require myohemoglobinemia for their genesis. The so-called "transfusion kidney" and the renal lesions in blackwater fever are striking examples. In such cases, too, a heme-bearing pigment, hemoglobin, is freed in the blood, and renal insufficiency is usually attributed to blockage of the tubules by the casts owing to the relative insolubility of hemoglobin in an acid urine. Since blocking of this sort is seen in the kidney of the crush syndrome and in myohemoglobinuria, a similar explanation has been evoked to account for the failure of kidney function in these disorders. In this view, the released pigment — whether hemoglobin or myohemoglobin — passes through the glomerular membrane and under conditions of acidosis is precipitated in the tubular urine, to form casts that block the further secretion of urine. A number of cogent arguments against

this hypothesis have, however, appeared during the past year. Ayer and Gauld[85] have pointed out that an identical pathologic picture is seen in the kidneys of severely jaundiced infants with congenital atresia of the bile duct in the absence of any sign of renal insufficiency. In addition, the blockage hypothesis implies some dilatation of the tubules and glomeruli proximal to the point of block, as is seen in obstruction by crystals of the sulfonamides. This is never seen in the renal lesion of the crush syndrome and of the transfusion reaction.[72] Bywaters[80] has noted that the scant urine was dilute in all his cases, contrary to one's expectation if mechanical obstruction were to account for the oliguria. Thus it seems that the idea of cast obstruction as the primary cause for the oliguria and renal failure in these conditions must be doubted. In fact, cast formation may be regarded as a phenomenon secondary to a markedly reduced glomerular filtration rate.[72, 83]

Whatever the mechanism by which renal failure is brought about, it seems likely that it is common to all these nephroses and that a substance toxic to tubular cells and interfering with renal hemodynamics is involved. It also seems clear that this hypothetical substance is derived from or through the agency of the heme-bearing pigment, for the pathologic picture is always seen when a heme-bearing pigment is at large in the blood and may be seen — in transfusion reactions, for example — in cases in which no tissue damage is apparent as a source of a toxic agent. Curiously enough, the heme-bearing pigments do not seem to be nephrotoxic in normal animals and in man. However, renal tubular lesions have followed the intravenous injection of heterologous myohemoglobin in the acidified rabbit[80] and of homologous methemoglobin in the acidified dog.[83] Ferrihemic acid, a breakdown product derived from methemoglobin, has also been used successfully to produce tubular damage in the dog.[86] Anderson, Morrison and Williams,[86,87] who claim that this substance, derived from the pigment of the malarial parasites, is responsible for the kidney lesion of blackwater fever, have expressed the opinion that it acts indirectly through vascular injury and thrombosis rather than directly on the tubular cells. There is much evidence, however, that the tubular cells are directly affected in all these nephroses. Anatomically, there is marked disorganization of the structure of these cells, especially those of the distal segment, and physiologically certain tubular functions, largely carried out in the distal segment, are gravely disturbed. It is noteworthy that acidemia, a prominent clinical feature, is necessary before the lesions can be produced experimentally. In addition, the urine remains highly acid, despite efforts to alkalinize it, both in man and experimental animals, once the condition has been established.[72] These facts suggest that the distal segment function of acidification may be involved in some fashion in the initiation and perpetuation of the renal lesion. The ability of the kidney to concentrate the glomerular filtrate, another distal segment activity, is also seriously interfered with, for the urine remains dilute despite the oliguria. Furthermore, there is evidence that the glomerular filtration rate and the renal blood flow are markedly reduced.[72, 83]

Therapy in these disorders remains largely empirical. Since the scanty flow of urine has heretofore been attributed to blockage by casts of precipitated pigment, it has seemed reasonable o increase water intake as a measure directed to washing out the casts and to alkalinize the urine in order to increase their solubility. In the light of the more recent work, the rationale of this therapy appears to be seriously weakened. It has, however, proved effective in practice, and until better methods based on more complete knowledge are developed, alkalinization and hydration will doubtless remain the procedures of choice. Bywaters[80] has emphasized the value of forcing fluids and of alkalinization in preventing renal insufficiency following compression injuries, and Smith and Evans[88] give enthusiastic support to these measures in blackwater fever. It is conceivable that hydration is of value because it may increase the decreased filtration rate, but no good evidence that alkaline therapy is beneficial has been adduced. Indeed, it is possible that alkalinization may be harmful,[72] although this point is highly controversial and awaits further experimental elucidation. Duncan and Blalock[79] have shown the efficacy of pressure in preventing local loss of fluid following crush injury, and this principle has found clinical application in the hands of Patey and Robertson,[89] who advocate elastic bandaging of the crushed extremity to prevent shock and the rapid return of toxic substances to the general circuit.

Bilateral Cortical Necrosis

In 1941, Duff and More[90] reviewed 71 cases of bilateral cortical necrosis reported in the literature and surveyed the experimental work on this subject. The disorder had been observed in 48 pregnant women and in 8 nonpregnant women and in 15 males from thirteen to sixty-four years of age. The necrotic lesions in the renal cortex had appeared in varying degree after a variety

of conditions. There seems to be common agreement that a toxic factor is to blame, and Duff and More believe that the actual effects in the vessels of the renal cortex vary with the degree of hypersensitivity of the vessels and with the intensity and duration of action of the toxic factor, stasis, thrombosis and marked vasoconstriction of the arteries of the renal cortex all playing more or less important roles. In the past year Sheldon and Hertig,[91] at the Boston Lying-in Hospital, have reported 2 cases that are typical in most respects of the clinical and pathologic picture. In each the disorder was observed following abruptio placentae and was characterized clinically by oliguria and anuria, with rapid progression to a fatal termination in uremia. The kidneys were increased in size, with multiple areas of necrosis in the cortical zone. The fundamental lesion consisted of degeneration in the wall of the afferent arteriole at the point of entry into the glomerular tuft, associated with local thrombosis and retrograde extension, resulting in multiple local infarction. Areas of necrosis were also found in other organs, and Sheldon and Hertig were impressed by the appearance of necrotic lesions in the anterior lobe of the pituitary gland in their cases, a finding that led them to believe that the condition was associated in some obscure manner with the endocrinal reorganization in pregnancy. Similar lesions have been produced experimentally in animals by many different methods, and in the past year Christensen[92] has found that cortical necrosis appears in white rats fed low-choline or choline-deficient diets.

The specific toxemia of pregnancy is usually considered to be a nephrosis complicated by hypertension that appears in the course of pregnancy, possibly on a congenital hypertensive background. Advances in this field have recently been discussed by Reid[93] in this series of medical-progress reports and will not be further considered here.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 29351

PRESENTATION OF CASE

First admission. A forty-two-year-old American salesman entered the hospital because of shortness of breath of one year's duration.

Twenty-one years before admission the patient had an attack of red, swollen joints that lasted five or six weeks and was followed by three months of semi-invalidism. He was well except for occasional stiffness of the joints until eleven years before admission, when he had another similar attack of rheumatism. Several teeth were removed following the attack, and he had had no joint troubles since then. One year before admission he first noted that he became short of breath easily and sweated profusely on the slightest exertion. This condition slowly increased in severity. Two months before entry he had several attacks of acute shortness of breath and consulted a physician, who prescribed digitalis (1 pill three times a day). About then he noticed swelling of the feet and ankles each morning. He continued to work until two weeks before admission, when he consulted another physician, who put him to bed.

Except for the attacks of rheumatism, his past history was negative. One sister died of heart trouble at the age of fifty-eight. His wife had had four pregnancies: the second ended in a miscarriage, in the third, premature twins died shortly after birth, and the other two children were living and well.

Physical examination showed a well-developed and well-nourished man with slight orthopnea but without cyanosis or dyspnea. There was slight engorgement of the neck veins. There were numerous moist rales and dullness at each base. The heart was greatly enlarged to the left, with a diffuse apical impulse at the fifth interspace, 14 cm. from the midsternal line. The right border was 3 cm. from the midsternal line. The rate was regular, and the sounds of poor quality, with a short, high-pitched systolic murmur at the apex. No diastolic murmur or thrill was heard. The liver was felt 3 to 4 cm. below the costal margin. The spleen was not felt. There was slight pitting edema of the ankles.

The blood pressure was 160 systolic, 110 diastolic. The temperature was 98.6°F., the pulse 80, and the respirations 21.

Examination of the blood revealed a red-cell count of 5,000,000, with a hemoglobin of 75 per cent, and a white-cell count of 11,300, with 61 per cent neutrophils. The urine was negative. A blood Hinton test was negative. An electrocardiogram showed normal rhythm, at a rate of 90, with left bundle-branch block and prominent T waves. A chest roentgenogram showed that the heart lay horizontally in the chest and was greatly enlarged, the enlargement chiefly involving the left ventricle. The pulmonary conus was prominent. The outline of the heart was indistinct because of a rather hazy type of dullness that involved the greater portion of the lungs and was most marked at the right base. The diaphragm was indistinct but appeared to be in the usual position and to move fairly well with respiration. The transverse diameter of the chest was 27.6 cm., and that of the heart 18.9 cm. — 6.1 to the right and 12.8 to the left.

The patient improved a great deal on rest, digitalis and ten daily injections of 50 per cent glucose, and was discharged after a period of two weeks. The haziness in both lung fields had definitely cleared.

Second admission (two and a half years later). The patient improved for a short time after discharge but then began to have spells of nocturnal dyspnea and slight orthopnea. The dyspnea increased and the edema became progressively worse so that he was confined to bed for a twenty-month period. His legs were tapped many times by his physician, who at one time removed 18 liters during a period of twenty-four hours. The chest was tapped three times. Salyrgan and other diuretics were given effectively. About one year before this admission the patient had improved somewhat and was able to sit around the house. He had had an abdominal tap about every two weeks during the previous year and had taken 3 gr. of digitalis a day (recently, 7½ gr. a day).

Physical examination showed that the heart was still greatly enlarged. The rate was variable; at times it was 60 and then quite suddenly jumped to somewhat over 80, with some extrasystoles. The sounds were poor, and no murmurs were heard. There were rales at the lung bases, and signs of fluid at the left base and in the abdomen. The liver was felt 11 cm. below the right costal mar-

*On leave of absence.

gin. There was tremendous porky edema of the legs, and considerable congestion of the neck veins.

The blood pressure was 130 systolic, 65 diastolic. The red-cell count was 5,480,000, with 80 per cent hemoglobin, and the white-cell count 11,800, with 86 per cent neutrophils. The serum protein was 7.3 gm. per 100 cc. An abdominal paracentesis yielded 6000 cc. of clear, straw-colored fluid. A left chest tap at the angle of the scapula in the seventh interspace yielded bloody fluid, which continued to be bloody and later became xanthochromic.

A chest roentgenogram showed marked enlargement of the heart involving all chambers, most marked in the region of the left ventricle. The right border had a double contour, probably owing to prominence to the right of the left auricle. The posterior mediastinum was also obliterated by auricular enlargement. The pulsations of the heart were extremely weak and diffuse fluoroscopically. When the patient was placed in a prone position the mediastinal shadow changed, becoming broader across the base. The aorta was of normal size. There was considerable air in the left pleural cavity. The left lung seemed about one quarter collapsed. There was also fluid in the left pleural cavity, the level being at the eighth rib in the anterior axillary line. The hilar shadows on both sides were grossly increased in width and density. There was a calcified lymph node in the right axilla. The electrocardiogram continued to show left bundle-branch block.

On the eleventh day a friction rub was heard at the apical area that was confined to diastole and did not disappear on full inspiration. The following day the rub was to-and-fro, being distinct in diastole and systole.

The patient responded to digitalis and diuretics and was discharged on the fifteenth hospital day.

Third admission (four and a half years later). After leaving the hospital the patient remained in bed for about six months but then was able to get up and around; he became very dyspneic on exertion although no more so than formerly. He always had to sleep on several pillows at night. During this interval he frequently accumulated fluid, which was controlled fairly well by diuretics of one sort or another. Three weeks before reentry he began having a cough productive of white frothy sputum; his legs began to swell, and the dyspnea became so severe that he re-entered the hospital.

Physical examination showed a pale, orthopneic man with labored respirations. There were diminished voice sounds, breath sounds and dullness over the left chest anteriorly and posteriorly. The apex impulse of the heart was not seen or felt. The left border of dullness was not made out. The aortic second sound was equal to the pulmonic. The heart sounds were of poor quality, with a rate of 40 at both apex and wrist; the rhythm was normal. There was heavy pitting edema with elephantiasis of both legs.

The blood pressure was 140 systolic, 80 diastolic. The pulse was 40, and the respirations 28.

The red-cell count was 4,800,000, with 90 per cent hemoglobin. The total protein was 6.79 gm. per 100 cc., with an albumin-globulin ratio of 1.54. An electrocardiogram showed a 2:1 block, with left bundle-branch block and left-axis deviation.

A chest roentgenogram showed marked change in the appearance of the heart. It had definitely increased in size, particularly in the region of the superior portion of the right ventricle, with the formation of a localized bulge in this area. There was fluid in the left chest, and slight displacement to the right.

The patient again responded well to digitalis and diuretics and was discharged in three weeks.

Fourth admission (fourteen months later). The patient returned for symptomatic relief of congestive failure.

Physical examination showed a pale man with rather marked respiratory difficulty sitting up in bed. There were moist rales, increased dullness and absent breath sounds over the left chest, both anteriorly and posteriorly, and medium moist rales over the right base. There were no further changes in the examination of the heart. The liver was felt four fingerbreadths below the costal margin. There was elephantiasis of both legs.

The blood pressure was 105 systolic, 55 diastolic. The red-cell count was 5,030,000, with 92 per cent hemoglobin, and the white-cell count 9200.

A chest roentgenogram showed fluid in the left pleural cavity displacing the heart to the left. The left border of the heart was incompletely visualized. An electrocardiogram showed auricular fibrillation, with complete block and right bundle-branch block.

The patient remained in the hospital for three weeks, on restricted fluids and diuretics, and lost 37 pounds of fluid.

Fifth admission (six months later). At home he continued to take digitalis but diuretics were administered with difficulty because of his poor veins. He had received not more than three intravenous administrations of Salyrgan in the interval and had been reduced to the rectal and intramuscular

use of this drug. He gradually accumulated a large amount of fluid and became much more dyspneic, even at rest.

Physical examination had not changed appreciably. There were marked ascites and peripheral edema. The heart rate was 40 and there were signs of pleural effusion on the left. An electrocardiogram showed auricular fibrillation with complete auriculoventricular block and left bundle-branch block, the ventricular rate equaling 40.

A chest roentgenogram showed that the heart had not appreciably changed. There was slightly more fluid in the left chest than previously and the pulmonary vessels appeared more engorged. There was the marked thickening of the pleura on the left that had been present on all the previous films. Fluoroscopy showed that the right ventricle was still unusually large in its upper portion.

On a regime of bed rest, digitalis, ammonium chloride and Salyrgan, the patient improved rapidly and lost 40 pounds of fluid. He was discharged in three weeks.

Final admission (two and a half years later, at the age of fifty-four). The patient was followed at home by his physician, receiving digitalis, ammonium chloride and Mercupurin, and did well under this regime until two months before admission, when he gradually began to retain fluids and developed increasing edema of the legs and breathlessness. Five days before entry he developed cough productive of pink, frothy sputum, and on the night before admission he became so orthopneic that he was unable to sleep and thought he was going to smother to death.

Physical examination showed a pale, extremely dyspneic man in marked congestive failure. The neck veins were markedly distended in the upright position. The chest was barrel shaped, with flatness to percussion and absent breath sounds in the lower left chest. On the right there were coarse, bubbling rales at the base. The heart was enlarged to the anterior axillary line, the sounds were distant, the rhythm was very irregular, but no murmurs were heard. The abdomen was distended and tympanitic. The liver was not enlarged to percussion and the spleen was not palpable. The peripheral edema extended to the groin.

The blood pressure was 105 systolic, 56 diastolic. The apex rate was 76.

The red-cell count was 5,150,000, with a hemoglobin of 16 gm., and the white-cell count 33,400, with 92 per cent neutrophils.

The patient failed to respond to the usual measures and died approximately twenty-four hours after admission.

Differential Diagnosis

Dr. William W. Beckman: In spite of the fact that many features of this case confused me when I went over it, I am relatively certain, because of the symptoms of dyspnea and edema, the physical signs of enlarged heart confirmed by x-ray and the electrocardiographic evidence of increasing conduction difficulty, that the patient was suffering from heart disease and, of course, that he had congestive failure. Dr. Paul D. White always teaches that one is supposed to make not only a functional diagnosis, which would be congestive failure, but also a diagnosis of the structural abnormality of the heart and of the etiology or the condition producing the structural and functional abnormalities.

So far as etiology is concerned, there are a number of things one need not consider because of the extreme duration of the congestive failure. The patient had some degree of congestive failure for thirteen years without any remissions. It is only necessary to mention congenital heart disease in passing. He might possibly have had an interventricular septal defect that ultimately led to left ventricular hypertrophy and failure; but it is unusual for congenital heart disease to wait for forty-two years to manifest itself. Also, the complete absence of cyanosis anywhere in the story is very much against a septal defect, because if the left ventricle fails the pressure in it falls below that on the right and unoxygenated blood is forced into the peripheral circulation to produce cyanosis. The same argument holds for cor pulmonale. The absence of cyanosis, polycythemia and evidence of right ventricular preponderance makes it unnecessary to give this diagnosis more than passing consideration. Again, the duration is too long for syphilis. Also there is no characteristic murmur of aortic regurgitation, and the serologic tests for syphilis were negative.

At the time of the first admission the patient had a blood pressure of 160 systolic, 110 diastolic, which represents true hypertension, and, as often happens, the first thing that drew attention to the high blood pressure was the presence of congestive failure. However, I do not believe that hypertension alone could account for this degree of failure extending over thirteen years, but it doubtless was a contributing factor.

Arteriosclerosis and coronary heart disease must also be considered. The presence of bundle-branch

block favors this diagnosis. The absence of characteristic T-wave changes in the electrocardiogram, and particularly the complete absence of mention of anginal pain anywhere in this long abstract, make the diagnosis of coronary heart disease untenable as the explanation for twelve years of congestive failure. I think the presence of pain in the joints is of significance in the etiology of the type of heart disease. In the first place, the way the attacks of joint pain are described is characteristic of rheumatic fever; it is much more like that than like rheumatoid arthritis. He had two distinct attacks of rheumatic fever and probably some activity between the attacks, as evidenced by the intermittent joint pains. Since it is well known that few people have two attacks of rheumatic fever without some heart disease, it is probable that he at least had myocarditis. Another thing in favor of rheumatic heart disease is the duration, for on the law of averages people who stay in congestive failure for prolonged periods of time have rheumatic heart disease oftener than any other type of heart disease. That, of course, is just on the basis of statistics and may mean nothing in this particular case.

Another thing in favor of rheumatic heart disease is the conduction difficulty, which ended in auricular fibrillation. Auricular fibrillation is one of the common features of rheumatic heart disease, particularly in cases in which there is mitral stenosis. Another thing that might be explained on the basis of rheumatic heart disease is the development of pericarditis. The patient may have had pericardial effusion at the time of the second admission, judging from the x-ray film. Later on during the admission he developed a definite friction rub, which seemed to be pericardial and not pleuropericardial. All this is in favor of rheumatic heart disease. Regardless of whether that was the fundamental thing, he doubtless had some residual myocardial fibrosis as the result of the previous attacks of rheumatic fever.

Strongly against the presence of rheumatic heart disease, however, is the complete absence of murmurs throughout the twelve years that the patient was followed, except for one occasion, at the time of his first admission, when they mentioned an apical systolic murmur to which no one attached significance. However, for no heart murmurs to have been heard is not incompatible with rheumatic heart disease, because all the reported examinations in this record were done when the man was in severe congestive failure. Frequently, in failure, one does not hear a murmur even though there is valvular disease. In favor of rheumatic heart disease is the x-ray evidence of an extremely large left auricle. The roentgenologists say that that is very good evidence for mitral stenosis. However, he did not show anything except two elevated white-cell counts to suggest true rheumatic activity during the twelve years. There was no prolongation of the PR interval, no joint pain or anything else that suggests rheumatic activity.

Against the whole thing's being on the basis of congestive failure is the fact that pleural effusion was always on the left side. We are taught that, if unilateral effusion is present as a part of heart failure, it is on the right side rather than the left. It was always on the left in this case. The fact that the fluid was bloody and xanthochromic is highly unusual for fluid in congestive failure, and suggests that some other process was present. However, it is known that the patient had had three chest taps shortly before that admission, and at the time of admission there was air in the chest, which may have indicated that previous taps had damaged the lung and had allowed blood to escape into the pleural space. We therefore cannot put too much weight on the bloody fluid.

I cannot fit two factors very well into the diagnosis of rheumatic fever. One is the fact that the patient showed a thickened pleura in all the films. Another thing is the bulge that developed on the right ventricle, as seen by x-ray. I think that this is a good time to have the x-ray films exhibited, because I need a lot of help from them.

DR. MILFORD SCHULZ: These are the films taken at the first and second admissions. They are all anteroposterior views. There are also a good many oblique views that we might have use for later.

DR. BECKMAN: Can you be sure that the left auricle was enlarged, or must you rely on the fluoroscopist?

DR. SCHULZ: In the right antero-oblique view there seems to be definite enlargement posteriorly in the region of the left auricle.

DR. BECKMAN: You are quite sure that it is the left auricle?

DR. SCHULZ: It is in the position that the auricle usually occupies. I think that the patient was undoubtedly fluoroscoped and that the person who interpreted the examination took the fluoroscopist's opinion into consideration.

DR. BECKMAN: Where is the bulge on the right ventricle?

DR. SCHULZ: This is the right antero-oblique film, and I believe that this represents the bulge in the area of the right ventricle anteriorly.

DR. BECKMAN: Do you suppose it could be an aneurysm?

DR. SCHULZ: It was not present previously. How frequently does an aneurysm occur in the right ventricle?

DR. BECKMAN: Almost never, but I have to explain it some way.

How about the prominence of the left auricle in the earlier films? Is it really the left auricle, or has it some connection with the later shadow in the ventricle?

DR. SCHULZ: I should say that it was the left auricle. This homogeneous increase in density may be fluid in the left chest. You can see it extending along the lateral chest wall. Or perhaps it is thickened pleura.

DR. BECKMAN: That was said to be present in all films, although they mentioned it only at the end.

DR. SCHULZ: It had been present since the time of the pneumothorax.

DR. BECKMAN: I do not know whether it is possible to say that the thickened pleura was due simply to the fact that the lung was traumatized and blood went into the thorax to cause sufficient irritation to give thickening. It may have been due to some other process, although I am at a loss to explain it.

I shall have to guess concerning the bulge in the right ventricle. As I have said, an aneurysm in this region is very uncommon. Aneurysms are usually the result of coronary heart disease with a cardiac infarct. At the admission prior to the one when the bulge in the right ventricle was noted, a friction rub was heard. This might possibly have been the result of infarct, perhaps even in the right ventricle, which thereafter led to weakening and subsequent development of an aneurysm. However, I do not believe that it is possible to make a diagnosis of coronary disease in the complete absence of precordial pain throughout the history, particularly at the time the rub appeared. There would have to be more evidence of coronary disease than he had to lead to the diagnosis of coronary occlusion.

The only other thing I can think of is a tumor in the right side of the heart. There are a wide variety of primary tumors, and every kind of metastatic tumor has been seen in the heart. I do not know how one can differentiate primary tumors of the heart, but I shall "stick out my neck" and say that this patient had a benign tumor in the right ventricle. I presume that he had mitral stenosis on the basis of the previous attack of rheumatic fever and the x-ray evidence of mitral stenosis, although a murmur was never heard. I believe that the lungs will show pulmonary edema. The white-cell count of 32,000 terminally means that he had some acute infection, probably bronchopneumonia. He might have had acute bacterial endocarditis, but there is no evidence for that, and I think pneumonia is far commoner in occurrence. I also think that there was cardiac cirrhosis of the liver on the basis of the fact that the liver was so large at the onset and was not palpable at the final admission.

DR. BENJAMIN CASTLEMAN: Dr. Williams, would you like to comment?

DR. CONGER WILLIAMS: I know the answer. There is just one thing that I should like to say. I remember seeing this patient on the ward when I was a house officer several years ago. At that time the diagnosis of coronary heart disease was questioned because of the duration of symptoms. It was also pointed out that the electrocardiogram, which then showed bundle-branch block, could very well conceal any underlying difference in preponderance of the ventricles. As soon as bundle-branch block appears, axis deviation is no longer significant. The new pattern bears no relation to ventricular preponderance and may conceal a high degree of right or left preponderance.

CLINICAL DIAGNOSES

Arteriosclerotic heart disease, with right and left congestive heart failure.

Pleural effusion, left.

DR. BECKMAN'S DIAGNOSES

Rheumatic heart disease, with mitral stenosis.

Congestive heart failure.

Thickened pleura, possibly due to hemothorax.

Bronchopneumonia.

Cardiac cirrhosis.

Benign tumor of right ventricle?

ANATOMICAL DIAGNOSES

Pulmonary arteriosclerosis, severe, arterial and arteriolar.

Ayerza's disease.

Pulmonary embolism, old, left (? thrombosis).

Mural thrombus of right atrium.

Cor pulmonale.

Organizing blood clot, left pleural cavity.

Mural endocarditis, fibrous.

Pericarditis, fibrous.

Bronchopneumonia.

Peripheral edema.

Passive congestion of liver, spleen and kidneys.

Pathological Discussion

Dr. Castleman: This man had an enormous heart, weighing 750 gm. The enlargement for the most part was on the right side. The right auricle was tremendously enlarged, and there was

Figure 1. *Photomicrograph of Lung Showing Arteriosclerosis.*

a mural thrombus in the appendage. The right ventricle was tremendously dilated and thickened, measuring 7 mm. in thickness, which is at least twice normal. The left auricle was not enlarged; neither was the left ventricle. We were unable to find any abnormalities in the valves. The ring of the tricuspid valve was greatly dilated, measuring 16 cm. in circumference. The pulmonary valve was also somewhat dilated, and the conus below it was markedly dilated, forming an aneurysmal outpocketing approximately 1 cm. deep. The endocardium over it was thickened and fibrous, but the underlying myocardium was normal. The appearance of the endocardium was similar to that seen below the aortic valve in the left ventricle in cases of long-standing aortic regurgitation. The coronary arteries showed only slight sclerosis. Grossly we were fairly certain that the etiology of the enlargement of the heart was in the lungs and not in the heart.

On examination of the pleural cavities we were amazed to find a large mass, about 9 by 8 by 8 cm., in the lower part of the left pleural cavity extending from the diaphragm up to the fourth rib. It was adherent to the pleura and pushed the left lower lobe medially and anteriorly; it also pushed the heart over a bit. This proved to be an organizing hematoma, which apparently must have occurred at the time of one of the chest taps before the second admission, as Dr. Beckman suggested. There was no fluid in the left pleural cavity. The lungs in gross showed a moderate degree of arteriosclerosis of the main vessels, but microscopically there was severe arteriolarsclerosis. This slide (Fig. 1) is a low-power view of a section of the lung showing three arteries with markedly thickened walls and intimal hyalinization. The intervening lung is normal. The next slide (Fig. 2) is a high-power view showing the luminal narrowing. The findings are those of the Ayerza syndrome and explain the right-sided cardiac hypertrophy. There was, in addition, a terminal

Figure 2. *Photomicrograph of High Magnification Showing a Vessel with Marked Luminal Narrowing.*

bronchopneumonia and a large, laminated, old, adherent embolus in the left main pulmonary artery and its two major branches, apparently arising from the mural thrombus in the right auricle. It may have originated in situ as a thrombus, but I believe that most cases of thrombosis of the large pulmonary arteries begin as emboli and build up by superimposed thrombosis. It was an old affair and had nothing to do with the terminal event; but it certainly added to the burden of the right heart. The liver showed moderate congestion but no cirrhosis.

I think the suggestion by Dr. Williams that the bundle-branch block disturbed the axis deviation certainly held here. If he not had it, there certainly would have been a marked right-axis deviation.

CASE 29352

Presentation of Case

A seventy-seven-year-old baker entered the hospital because of severe dyspnea.

Approximately twenty or thirty years prior to admission the patient began to suffer with mild dyspnea on exertion that became progressively worse. About four and a half years before entry he was seen in the Out Patient Department, where a few wheezes and rales were heard in his chest. The heart sounds were distant. The aortic second sound was greater than the pulmonic; there were no murmurs. The blood pressure was 140 systolic, 85 diastolic. He complained of moderate urinary frequency. The diagnoses of pulmonary emphysema, arteriosclerotic heart disease and early decompensation were made. He was digitalized, with improvement of his symptoms. After that he was quite well, except for a chronic cough productive of small amounts of gray sputum daily, until one month prior to admission, when he developed epigastric pain, gas and constipation. Because of the constipation his physician stopped digitalis and referred him for gastrointestinal studies. He rapidly became dyspneic and orthopneic. He had no nocturnal attacks or chest pain. The chronic cough became worse, and the patient raised one cupful of gray sputum daily. There was no nausea, vomiting, anorexia or tarry, bloody or clay-colored stools. There was no fever, hemoptysis, weight loss or chills.

The family and past histories were noncontributory.

Physical examination revealed a well-preserved old man who sat up in bed because of moderate dyspnea. He coughed frequently and brought up small amounts of foul-smelling, yellow sputum. The chest was hyperresonant. The heart was percussed 10.5 cm. to the left of the midsternal line in the fifth intercostal space. The sounds were distant and there were many extrasystoles. There was a soft, blowing systolic murmur over the entire precordium and in the left axilla but best heard at the apex. The neck veins were slightly distended. There was slight dullness at the base of the left chest posteriorly, and in that area the voice and breath sounds were slightly suppressed. The abdomen was soft; no masses were felt, and no tenderness elicited. There was pitting edema at the ankles.

The blood pressure was 120 systolic, 70 diastolic. The temperature was 99°F., the pulse 90, and the respirations 25.

Examination of the blood revealed a red-cell count of 4,500,000, with a hemoglobin of 14.5 gm., and a white-cell count of 7500, with 75 per cent neutrophils. The urine and stools were negative. A blood Hinton test was negative. The serum protein was 6.3 gm., and the nonprotein nitrogen 70 mg. per 100 cc.; the carbon dioxide combining power was 21.0 millimols, and the chloride 97.5 milliequiv. per liter.

A gastrointestinal series was negative. Chest roentgenograms showed haziness over almost all of both lung fields consisting of strand-like infiltration following the pathway of the bronchovascular tree. In addition, in the right lower lobe there was an area of increased density 5 cm. wide and 3 cm. high, with indefinite margins. There was calcification of some of the hilar lymph nodes on the right. There was a small amount of fluid in the left pleural cavity, and probably some in the right. The heart was enlarged, especially in the region of the left ventricle, and the aorta was tortuous.

An electrocardiogram showed a normal sinus rhythm of 75. The PR interval was 0.16 second. The ST segment was depressed in Leads 1, 2 and 4. The T wave was low in Leads 1, 3 and 4, and there was slight left-axis deviation.

The patient was digitalized and given mercurial diuretics, following which the edema lessened. On the ninth hospital day oliguria developed and the nonprotein nitrogen was found to be 116 mg. per 100 cc. The nonprotein nitrogen gradually rose, and complete urinary suppression developed on the eleventh hospital day. Catheterization yielded only 2 cc. of urine. He was given Mercupurin and 50 cc. of 50 per cent glucose solution. On the thirteenth hospital day the nonprotein nitrogen was 160 mg. per 100 cc., the carbon dioxide combining power 19.7 millimols per liter and the chloride 93.2 milliequiv. per liter. The patient showed increasing signs of uremia, remained anuric for four days and died on the fifteenth hospital day.

Differential Diagnosis

Dr. Jacob Lerman: I should like to know what the urine showed, even though it was said to be negative.

Dr. Benjamin Castleman: At the first examination it was amber and alkaline, with a specific gravity of 1.025, and showed no albumin or sugar. The Sulkowitch test for urinary calcium was ++. On the following day the specific gravity was 1.010, and on the fifth day 1.007; there were no other changes.

Dr. Lerman: The diagnoses made in the Out Patient Department — arteriosclerotic heart disease, cardiac failure and pulmonary emphysema — seem justified on the basis of the findings at

that time. The patient's condition remained unchanged until he developed evidence of pulmonary infection. At that point we may say that, as so commonly happens in people with long-standing congestive failure, chronic bronchitis developed. Later he developed epigastric pain, which suggested to the doctor the need for gastrointestinal studies.

The physical findings indicate a dilated heart with congestive failure and fluid in the left chest. The electrocardiogram suggests obvious digitalis effect and slight coronary disease. The blood findings are normal. To me the striking laboratory findings are the retention of nitrogen and the mild acidosis in the presence of an apparently normal urine. The specific gravity was 1.025, indicating fairly good concentration, at least in the beginning. X-ray study confirmed congestive failure and showed something else, which may have been a pulmonary tumor.

Dr. Milford Schulz: These films show a somewhat enlarged heart with particular prominence in the left ventricular area. There is some fluid at both bases, and the hilar and pulmonary markings are increased. In addition, this area of infiltration apparently lies in the midportion of the right lower lobe.

Dr. Lerman: Is the area in the right lower lobe consistent with bronchiectasis, or is it not extensive enough?

Dr. Schulz: Some of the markings at the bases are consistent with bronchiectasis. I think the area of infiltration is something more recent — perhaps an infarct.

Dr. Lerman: The x-ray findings are consistent with congestive failure plus the additional shadow in the right lower lobe, which Dr. Schulz suggests may be a pulmonary infarct. It may be a tumor. Certainly the clinical findings are consistent with bronchiectasis at both bases in a man with long-standing congestive failure.

The point I must explain is why this patient had renal failure in the presence of a normal urinary picture. It seems difficult. I cannot see any connection between the shadow in the right lower lobe and the renal involvement. The x-ray findings of an apparently prominent left ventricle and the accentuated aortic second sound noted in the record suggest the existence of hypertensive heart disease. We have no evidence from the record that he had hypertension, and it does not seem likely that a slight degree of congestive failure existing four and a half years before entry could have dropped the blood pressure from a hypertensive to a normal level. Therefore, I doubt that he had hypertensive heart disease. Arteriosclerotic heart disease is the more likely explanation of the cardiac picture.

I should like to consider chronic glomerulonephritis as an explanation of renal failure. It is most unlikely that he would not have albuminuria or show slight evidence of nephritis in the sediment. Furthermore, the concentration of the urine to 1.025 is hardly consistent with chronic glomerulonephritis. There is no obvious evidence of arteriolar nephrosclerosis or of pyelonephritis. The absence of hypertension certainly argues against glomerulonephritis, nephrosclerosis and pyelonephritis.

The final episode of oliguria and anuria could have been due to the natural course of uremia, but we must remember that he was taking mercurial diuretics and that these may have caused additional irritation of the kidneys and contributed to their final shutdown. I am inclined to believe that at autopsy there was evidence of irritation of the kidneys due to the diuretics. This, however, does not help to explain the discrepancy between renal failure and normal urinary findings. Cardiac failure alone does not explain it. Cardiac failure plus pulmonary infection in the presence of arteriosclerotic kidneys might explain the picture.

Other mechanisms, extrarenal in origin, may produce renal failure without actual injury of the kidneys. Dehydration is one of them, but it obviously does not play any role here. Adrenal failure sometimes causes marked nitrogen retention without renal damage. I have never seen this degree of renal failure — a nonprotein nitrogen of 70 mg. per 100 cc. and a carbon dioxide combining power of 21 millimols per liter — in adrenal disease. Moreover, the blood chloride was within normal range, and there was no hypotension.

One should consider some process involving both ureters simultaneously. Infection may do it, but there is no evidence of it here. I cannot conjure up anything else, — malignant disease or any other pathologic process, — that would involve both ureters uniformly. One would have to assume that the patient had congenital absence of one kidney or of one ureter with involvement of the remaining kidney or ureter by a malignant process, such as retroperitoneal lymphoma. This seems somewhat farfetched.

One must also consider bilateral ischemia of the kidneys. Among the possible causes of this condition is some disturbance of the aorta itself. Aneurysms, in the proper location, have been described that produce progressive ischemia of the kidney with renal failure and eventual shutdown. This patient had pain in the epigastrium. He may have had a dissecting aneurysm of the thoracic aorta that worked its way down to both renal arteries and then caused progressive shutdown. Against this diagnosis is the fact that the pain

was not excruciating and did not persist. Furthermore, there was no evidence of arterial involvement elsewhere: there is no mention of obstruction of the iliac arteries.

One might consider a horseshoe kidney as a cause of progressive renal failure without much in the way of urinary findings. However, since there is no mention of an abdominal mass we need not consider it further.

It seems to me that the most likely diagnosis is arteriosclerotic heart disease with congestive failure, and arteriosclerotic kidneys with renal failure resulting from congestion plus the toxic effect of chronic pulmonary infection. I meekly add the possibility of an aortic aneurysm producing bilateral renal ischemia.

Clinical Diagnosis

Arteriosclerotic heart disease, with decompensation.

Dr. Lerman's Diagnoses

Arteriosclerotic heart disease, with congestive failure.

Uremia due to congestion of arteriosclerotic kidneys plus toxic effect of chronic pulmonary infection.

Bilateral renal ischemia due to aneurysm of aorta?

Anatomical Diagnoses

Undifferentiated malignant tumor involving retroperitoneal lymph nodes, lungs, pleura, spleen, peritoneum and vertebral bone marrow.

Compression of both ureters by tumor.

Hydroureter, right.

Hydronephrosis, right.

Cardiac hypertrophy, moderate.

Pathological Discussion

Dr. Castleman: At autopsy this man showed perfectly normal-looking kidneys, except for slight scarring such as one might expect to find in a man of his age. The right pelvis was dilated, but the left was not. The retroperitoneal nodes all along the aorta were enlarged, were replaced by tumor and compressed both ureters, the right more than the left. We were unable to get a probe into the right ureter at a point about 6 cm. below the ureteropelvic junction. A similar process was present on the left, but the occlusion was not so complete because it was easily probed. However, with the probe out, the walls of the ureter closed down on the lumen, so that during life there was probably complete obstruction. It is possible that the complete occlusion on the right side produced so-called "reflex anuria" on the other side so that no urine reached the bladder, but the urologists inform me that this rarely, if ever, occurs.

The shadow in the right lower lobe was a markedly thickened pleura infiltrated with neoplasm. There were nodules of tumor in the lung parenchyma, in the spleen, in the omentum and in the mesentery; and microscopically they were present in the vertebral bone marrow. The strand-like infiltration observed on the roentgenogram was due to tumor infiltration of the lymphatics.

The exact classification of the tumor is difficult. The cells are large, many with two or three nuclei, and although it suggests in a few places an embryonal form of carcinoma, such as is seen in the testis, it is probably some form of undifferentiated sarcoma. The testes were normal, and we were unable to find any other primary source, so that we shall have to leave it as an undifferentiated malignant tumor.

The heart was moderately enlarged and showed minimal coronary disease. There was no evidence of disease within the kidney itself.

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INFECTIOUS DISEASE IN WARTIME

The current educational campaign of the Metropolitan Life Insurance Company has for its subject, suitably enough under present conditions, rheumatic fever. To achieve the objectives of an earlier recognition of rheumatic fever, better care of the child ill with the disease, and an appreciation of the increased dangers resulting from overcrowding and the unsanitary conditions following in the wake of our organization for war, the company has planned a most comprehensive program. This includes the distributing of suitable material to policyholders and others, the enlisting of the interest of local physicians and school officials and the arranging of discussions at parent-teacher associations, service clubs and so forth. In addition, an excellent pamphlet on the clinical considerations of rheumatic fever has been prepared for distribution to physicians. In this country the best approach to any public problem is still the education of the public.

Rheumatic fever remains a major health problem today. Between the ages of five and nine years it causes more deaths than any other single disease, and is exceeded in mortality only by a combination of the four principal communicable diseases of childhood. Between the ages of ten and fourteen years it is also outranked by none, and between fifteen and twenty-four years it is led only by tuberculosis. It is fair to say, however, since the inference may be drawn that rheumatic fever is actually on the increase, that its relative growth in importance is due to the fact that deaths from other diseases have declined even more rapidly. Actually the death rate from chronic heart disease among the company's policyholders between the ages of five and twenty-four has fallen two thirds in the last thirty years, and that due to acute rheumatic fever at approximately the same rate — from 7.2 to 1.7 per 100,000.

The disease rheumatic fever has richly earned the significance that is being attached to it and the efforts that are being made to defeat it. There is, however, reason to doubt that at the present time any important infectious disease is undergoing a drop in its morbidity rate. In the armed forces, composed largely of men under thirty and including such a large proportion of the group in the later years of adolescence, rheumatic fever constitutes a constant and relatively serious medical problem. Everyone is aware of the increase in communicable diseases, particularly of scarlet fever, — fortunately in a mild form, — of meningitis and of pulmonary infections.

The same general experience obtained during World War I, and it is, of course, common knowledge that war with its mass movements of population, its mobilization in close quarters of large

numbers of susceptible individuals and its tendency to break down the usually well-organized civilian health facilities, carries with it an inevitable increase in the microscopic enemies of man, regardless of the justice of the cause to which the Nation is committed.

For some time to come the acute infectious diseases must be combated — as they have been for years; and it is hoped that more effective weapons will be available than have ever before been possessed. There is every indication, also, that outbreaks of malaria and other tropical and semitropical diseases must be faced when the troops return from their far-flung battle lines.

A NURSE ON BATAAN AND CORREGIDOR

LIEUTENANT REDMOND,* formerly an American Red Cross nurse, now an officer in the Army Nurse Corps, went to Manila in September, 1940, after three years of service in the Army and Navy Hospital at Hot Springs, Arkansas. Little did she realize what her experiences would be when, after a year, she found herself in the Sternberg General Hospital in the fall of 1941. Her wards were going like clockwork at seven o'clock in the morning of December 8 when she came off duty, and she had planned a morning of sleep and an afternoon of golf. The attack on Pearl Harbor, when reported over the telephone by a friend, was at first taken as a joke, but by some sensible instinct she rushed to the bank and cabled her savings home. No sleep came that day and for many days to come. Soon hundreds of casualties arrived in trucks, ambulances, buses, carts and anything that had wheels. Many were dead when they reached the hospital. Operating tables were empty hardly a moment at a time. The morale was magnificent. The wounded were quiet. Often one would say, "Take my buddy, he's hurt worse than me."

The bombing continued. Nurse Redmond watched some dogfights in the sky and saw three enemy planes brought down. The pilots, dead, were brought to the hospital; one was a German. Cavite was burning. Soon rumors spread, only to be followed by Japanese troops marching on Manila. By December 23, Nurse Redmond and her associates had been moved to Bataan. There she remained, conscious of the slowly approaching danger but always doing her full duty. Supplies grew short, the field hospitals were bombed, the dust and heat were indescribable. With a hospital full of dysentery patients, they had no lime for the latrines. Serum for gas gangrene ran out, and Colonel Adamo's patients had to be transferred to a hill away from the hospital sheds. Finally came the air raids, blowing some of the wards to bits. Foxholes were dug outside each building and used by all who could get to them; others crawled under the beds in the orthopedic ward after the traction ropes had been cut. Then came the care of the twice wounded. Fortunately Nurse Redmond was uninjured, although knocked down and buried in debris. Little work could be done for a day or two, except to bury the dead.

Like most persons in a crisis, one begins to think "long thoughts," and Nurse Redmond was no exception.

> That night we stayed in our fox holes. I didn't sleep. We hadn't eaten since breakfast, but I wasn't hungry. We were like hunted animals, waiting for the kill, almost hoping it would happen quickly so that the torment of waiting would end. But stronger than that was anger; anger and hate and a hot desire to fight back, to avenge our dead.
>
> What kind of human beings would deliberately bomb a hospital, defenseless, openly marked for what it was, filled with the wounded and the sick?
>
> I don't know. The only answer I had found when I crawled out of my hole in the morning, my head aching, a crick in my back, my legs cramped, was not an answer but a conviction. This isn't a war in which anybody — anybody — is let off. Each single individual of us is in it and each must give everything he has to give. An enemy that will bomb hospitals and undefended cities — sick and injured men, or women and children and helpless old people — isn't an enemy you can ever come to terms with; not in the usual meaning of the phrase. The war must end without compromise.

After more horrors, Bataan fell, and on April 7, Nurse Redmond was moved to Corregidor. There

*Redmond, J. *I Served on Bataan*. 167 pp. Philadelphia and New York: J. B. Lippincott Company, 1943.

she worked in a hospital tunnel, always cheerful, always doing what she could to serve her patients. There were some amusing moments. Food was better at first than on Bataan. A cleaning woman found some soap and nail polish, so the nurses had shampoos, finger waves and manicures. Some dresses were discovered, and they had a rummage sale. A Chinese tailor who had taken refuge in the tunnel proved to be a great find. He fashioned suits out of discarded officers' clothes, so the nurses had streamlined coveralls, skirts and blouses. Finally came the shelling of Corregidor, and even Nurse Redmond found it hard to face great numbers of people torn and bleeding and dying in masses: "When *one* patient dies it is agonizing enough; when you are faced by such mass suffering and death something cracks inside you, you can't even be quite the same again."

At last came the trip by air to Melbourne, Australia, leaving Corregidor on a strangely quiet night when the Japanese were celebrating the Emperor's birthday. General Wainwright's car led the small procession to the docks. The flight to Australia was as smooth and peaceful as if there were no war.

MEDICAL EPONYM

Clutton's Joints

This disease is described by H. H. Clutton in a paper "Symmetrical Synovitis of the Knee in Hereditary Syphilis" appearing in the *Lancet* (1: 391–393, 1886), from which the following is quoted:

> To recapitulate . . . one would say that the synovitis was symmetrical, affecting only the knees, that it was of a chronic and painless character, and that all the patients were the subjects of hereditary syphilis. . . . It is probable that, with further observation, the knees will not be found to occupy this solitary distinction, and that other joints will be seen to be affected in a similar manner. . . .

R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BLAKE — John B. Blake, M.D., of Brattleboro, Vermont, died August 17. He was in his seventy-eighth year.

Dr. Blake received his degree from Harvard Medical School in 1891. He taught there for a number of years and wrote on medical subjects. He was formerly surgeon-in-chief of the Boston City Hospital, visiting surgeon for the Long Island Hospital and consulting surgeon for the Boston Insane Hospital. He had been retired since 1920. He was a member of the Massachusetts Medical Society, American Medical Association, Boston Society for Medical Improvement, Boston Medical Library, Boston Surgical Society, Boston Obstetrical Society and American Surgical Association.

Two daughters and four sons survive.

SEED — Raymond C. Seed, M.D., of Lawrence, died June 6. He was in his forty-sixth year.

Dr. Seed graduated from Dartmouth College and received his degree from Jefferson Medical College of Philadelphia in 1921. He was a member of the Massachusetts Medical Society and the American Medical Association.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

TONSILLECTOMY AND POLIOMYELITIS

The Massachusetts Department of Public Health recommends the temporary postponement of tonsillectomies until an estimate can be made of the probable prevalence of poliomyelitis during the present season. Early indications pointed to a light year, but with cases on the increase in Connecticut and Rhode Island and a few cases in Massachusetts, some increase in prevalence in this state may occur. In epidemic years, numerous cases are usually reported before the middle of August. Because only a single case was recorded in the first two weeks of August, making a total of only 17 cases for the year, a large outbreak is not expected.

There is definite evidence that the bulbar form of poliomyelitis is likely to occur following tonsillectomy. The additional threat to life from this form justifies the postponement of such operations.

CHANGE IN PREMARITAL BLOOD-TEST LAW

As of June 12, 1943, a new premarital blood-test law became effective in Massachusetts. The underlined portions of the following copy of the law are called to the special attention of all physicians:

> *Section 28A*: Except as hereinafter provided, a certificate shall not be issued by the clerk or registrar under Section 28 until he has received from each party to the intended marriage a medical certificate signed by a qualified physician registered and practicing in the commonwealth, *a physician registered or licensed to practice in any other state of the United States* or a

commissioned medical officer on active service in the armed forces of the United States who has examined such party as hereinafter provided. *Such examination shall be made only to ascertain the presence or absence of evidence of syphilis, and shall include a serological test for syphilis.* Said test shall be made by a laboratory of the state department of public health or by a laboratory meeting standards approved by said department, or, if not located within the Commonwealth, approved by the United States Public Health Service. *The examination by such physician and the laboratory test shall be made not more than thirty days before a certificate is issued under Section 28.* If such physician, in making such examination, discovers evidence of any such disease, he shall inform both parties to the intended marriage of the nature of such disease and of the possibilities of transmitting the same to his or her marital partner or to their children. . . . Blank forms of medical certificates required under this section shall be furnished to city and town clerks by the Department of Public Health. . . . In emergency cases where the death of either party to the intended marriage is imminent or where the female is near the termination of her pregnancy, upon the authoritative request of a minister, clergyman, priest, rabbi or attending physician, the clerk or registrar may issue a certificate under Section 28 without having received the medical certificate, or having endorsed on his certificate a statement of such receipt, as provided by this section. Whoever, being subject to the laws of the commonwealth fails to comply with any provision of this section shall be punished by a fine of not less than ten nor more than one hundred dollars.

If the parties to the intended marriage reside in different communities in Massachusetts, the certificates should be made out in duplicate. In all other cases one certificate for each party is adequate.

DISTRICT OFFICES

With the opening of three new offices, all the eight districts of the Massachusetts Department of Public Health now have facilities where personnel assigned to the districts can meet for conferences and have a common repository for their records. Each district health officer now has a staff composed of nurses, engineers, nutritionists, social-service workers and others, and is equipped to assist physicians, boards of health and other agencies in solving problems connected with public health.

The location of these district officers and the names of the district health officers are as follows:

Southeastern District:
Dr. Harold W. Stevens
105 William Street, New Bedford
Tel. New Bedford 3–7081

South Metropolitan District:
Dr. Henry M. DeWolfe
1245 Hancock Street, Quincy
Tel. GRAnite 5006

North Metropolitan District:
Dr. A. Daniel Rubenstein
519 State House, Boston
Tel. CAPitol 4600 (Line 312)

Northeastern District:
Dr. Robert E. Archibald
367 Main Street, Wakefield
Tel. CRYstal 1118

South Central District:
Dr. Oscar A. Dudley
476 Main Street, Worcester
Tel. Worcester 2–8805

North Central District:
Dr. Arthur E. Burke
Central Avenue, Ayer
Tel. Ayer 2305

Connecticut Valley District:
Dr. Walter W. Lee
278 Main Street, Greenfield
Tel. Greenfield 3061

Berkshire District:
Dr. Walter W. Lee
184 North Street, Pittsfield
Tel. Pittsfield 2–1929

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JULY, 1943

Résumé

Diseases	July 1943	July 1942	Seven-Year Median
Anterior poliomyelitis	1	9	4
Chicken pox	398	436	402
Diphtheria	7	21	14
Dog bite	1150	1227	1199
Dysentery, bacillary	2	0	11
German measles	469	212	60
Gonorrhea	355	413	389
Measles	1468	1159	1159
Meningitis, meningococcal	62	13	5
Meningitis, other forms	7	7	*
Meningitis, undetermined	3	0	*
Mumps	244	555	431
Pneumonia, lobar	93	100	155
Salmonella infections	19	9	9
Scarlet fever	440	330	257
Syphilis	363	427	424
Tuberculosis, pulmonary	214	314	292
Tuberculosis, other forms	19	22	28
Typhoid fever	6	4	5
Undulant fever	7	4	4
Whooping cough	317	882	521

*Pfeiffer-bacillus meningitis only other form reportable previous to 1941.

Comment

The outstanding feature of the July communicable disease picture is the poliomyelitis figure, with only 1 case reported for the month; hence the chances of a sizable outbreak seem rather remote. Incidentally, this is the lowest number of recorded cases for July so far as this disease is concerned. Meningococcus meningitis, although still at a point twelve times as high as that of the seven-year median, has experienced a 33 per cent drop since June. Scarlet fever, which reached epidemic proportions during the previous months, is now well on its way down to more satisfactory levels.

Geographical Distribution of Certain Diseases

Anterior poliomyelitis was reported from Wakefield, 1; total, 1.

Diphtheria was reported from: Boston, 1; Cambridge, 1; Dennis, 1; Everett, 1; Fall River, 2; Woburn, 1; total, 7.

Dysentery, bacillary, was reported from: Boston, 2; total, 2.

Encephalitis, infectious, was reported from: Barnstable, 1; Brockton, 1; Cambridge, 1; Everett, 1; total, 4.

Malaria was reported from: Camp Edwards, 1; Fort Banks, 6; Fort Devens, 4; Millbury, 1; Whately, 1; total, 13.

Meningitis, meningococcal, was reported from: Ashland, 1; Auburn, 1; Barnstable, 1; Boston, 16; Bourne, 1; Brookline, 1; Cambridge, 3; Camp Edwards, 2; Canton, 1; Fall River, 3; Fitchburg, 1; Fort Banks, 1; Fort Devens, 2; Haverhill, 3; Holyoke, 3; Longmeadow, 1; Lowell, 1; Lynn, 1; Malden, 2; Methuen, 2; Pittsfield, 2; Quincy, 1; Rockland, 1; Somerville, 1; Springfield, 2; Stoneham, 1; Templeton, 1; Wakefield, 1; Watertown, 1; Weymouth, 1; Wilmington, 1; Worcester, 2; total, 62.

Meningitis, other forms, was reported from: Boston, 3; Chelsea, 1; Fall River, 1; Melrose, 2; total, 7.

Meningitis, undetermined, was reported from: Braintree, 1; Cambridge, 1; Worcester, 1; total, 3.

Salmonella infections were reported from: Boston, 2; Braintree, 1; Brookline, 2; Cambridge, 1; Grafton, 1; Lawrence, 2; Methuen, 1; Norwood, 1; Peabody, 2; Pittsfield, 1; Salem, 4; Spencer, 1; total, 19.

Septic sore throat was reported from: Beverly, 1; Boston, 5; Williamstown, 1; total, 7.

Tetanus was reported from: Brockton, 1; total, 1.

Trachoma was reported from: Boston, 1; total, 1.

Trichinosis was reported from: Boston, 2; Dover, 1; total, 3.

Tularemia was reported from: Falmouth, 1; Waltham, 1; total, 2.

Typhoid fever was reported from: Boston, 1; Fall River, 1; Holyoke, 1; North Attleboro, 1; Salisbury, 1; Saugus, 1; total, 6.

Undulant fever was reported from: Adams, 1; Boston, 1; Gloucester, 1; Hawley, 1; Merrimac, 1; Spencer, 1; Sudbury, 1; total, 7.

BOOK REVIEWS

Changes in the Knee Joint at Various Ages, with Particular Reference to the Nature and Development of Degenerative Joint Disease. By Granville A. Bennett, M.D., Hans Waine, M.D., and Walter Bauer, M.D. 4°, cloth, 128 pp., with 9 illustrations and 31 plates. New York: The Commonwealth Fund, 1942. $2.50.

As the authors state in their preface, the rheumatic disorders rank foremost among the crippling diseases and are a frequent cause of prolonged morbidity. The origin and exact characteristics of these disorders are imperfectly understood. Baring the chance discovery of a specific substance or some special method of treatment, it seems that the most promising approach to the problems that these disorders present is the one chosen by the authors. It is a fundamental necessity to know what goes on in apparently normal joints as age advances before one can even make shrewd guesses concerning the exact causes and the exact nature of the pathologic changes that are responsible for abnormal joints affected by any chronic progressive disease of uncertain etiology. The authors of this clearly written and beautifully printed and illustrated volume speak with authority derived from a complete familiarity with the extensive literature of the rheumatic disorders for the last one hundred years, a sound pathological training and a long clinical experience in the treatment of these disorders.

Investigation of the changes in the human knee joint at various ages was initiated by Bauer and Bennett in 1933. Their purpose was to familiarize themselves with the appearance of and the changes in the so-called "normal" joint as life goes on by studying these joints at each decade of life. The material was obtained post mortem or from amputations and was limited to those joints in which, so far as they could establish the fact, there had been no history or clinical evidence of arthritic disease. They found that all the joints obtained from individuals beyond the second decade of life exhibited alterations similar to those observed in hypertrophic arthritis (degenerative joint disease). The authors concluded that the articulations remain normal for only a very short time after maturation. They state: "Why this is so remains a riddle, as does the whole process of aging. . . . Because of the wide distribution of degenerative joint disease, it is evident that the disease is not climatically limited nor confined to the human species."

Their material consisted of sixty-three knee joints from persons ranging in age from one month to ninety years. In none of these joints in life had there been any symptoms of joint disease, and no abnormalities had been noted in clinical examinations. However, in every subject beyond the age of fifteen some degeneration was found in one or more tissues of the joints.

In the sixth decade the loss of all articular cartilage from an eburnated epiphysis was observed. Apparently the degree of villous hypertrophy and of synovial fibrosis was not proportional to the degree of change in the cartilaginous surfaces of the joints. In several specimens the synovial membranes were practically normal. In the seventh decade it was rare to find any one of the articular structures entirely normal. Typical marginal lipping was very frequent, and the semilunar cartilages were badly damaged. In the eighth decade large areas of complete absence of articular cartilage were found on the weight-bearing surfaces of the femur and of the tibia. These changes were still out of proportion to the changes in the synovial membrane, but the semilunar cartilages showed more fraying and partial calcification. In the ninth and tenth decades all these changes were more advanced.

Chapter IV, in which the authors give their interpretation of these articular findings, does not lend itself to abstract and should be read in toto. It is evident that they have become convinced that the reparative powers of hyaline articular cartilage are extremely limited and that, if necrosis occurs, it is replaced by imperfectly formed fibrocartilage. The subchondral bone suffers in like manner and concomitantly with the articular cartilage.

In Chapter V the authors' concepts of pathogenesis are given. They were arrived at not only as a result of this detailed visual study of the changes in normal joints but from their previous sound research work and their wide clinical experience. The authors appear to have assumed an entirely dispassionate attitude, which is admirable and rather rare. They have presented the evidence and carefully weighed its value, especially in relation to etiology. It is unfortunate that war service has made it temporarily

impossible for this brilliant teamwork to follow closely the elusive but fresh scent that certain unpublished research has already provided.

The Biological Action of the Vitamins. A symposium edited by E. A. Evans, Jr., Ph.D. 8°, cloth, 227 pp., with 36 illustrations and 8 tables. Chicago: The University Press, 1942. $3.00.

This is an outstanding collection of papers on recent fundamental investigations regarding the vitamins. The fourteen contributions included were presented at the University of Chicago in September, 1941, in co-operation with the University of Wisconsin, and a like symposium was given at Madison on respiratory enzymes. The volume contains papers on the biologic action of the vitamins in general, including cocarboxylase, thiamine, riboflavin, nicotinic acid, pyridoxine, pantothenic acid, biotin and vitamin K. The contributors include some of the most eminent workers in their fields, notably C. A. Elvehjem, Paul György, Norman Jolliffe, D. W. MacCorquodale and Vincent du Vigneaud.

In general outlook these papers consider not only the chemistry of the vitamins and their ration to experimental and clinical deficiency states, but also their rapidly unfolding roles in the field of the respiratory enzymes, in carbohydrate metabolism and in promoting the growth of yeasts and bacteria. For example, they point out that riboflavin is a prosthetic group in coenzyme II, which aids in catalyzing the oxidation of hexose monophosphate, and that it is essential for the growth of lactic acid bacteria; that the enzyme cocarboxylase, concerned in the decarboxylation of alpha keto acids, is an ester of thiamine; and that biotin has been found identical with coenzyme R, a compound necessary for the growth of certain nitrogen-fixing bacteria, and also with protective factor X or vitamin H, which inhibits the harmful effects of feeding raw egg white to certain animals.

Perhaps the most fascinating paper is that of du Vigneaud on biotin, which recounts the most recent chemical triumph in the field of vitamins. All are well worth reading, however, and this book is highly to be recommended.

The Hemorrhagic Diseases and the Physiology of Hemostasis. By Armand J. Quick, Ph.D., M.D. 8°, cloth, 340 pp., with 24 illustrations and 9 tables. Springfield, Illinois: Charles C Thomas, 1942. $5.00.

The past five years have witnessed great clarification in the mysteries surrounding the various problems relating to blood clotting. In this period a number of seemingly unrelated investigations have converged: new knowledge regarding prothrombin and methods for its detection, the discovery of the antihemorrhagic vitamin K, the purification and therapeutic use of heparin, and the discovery in sweet-clover disease of cattle of the hemorrhagic factor dicoumarol. In these investigations the name of Quick has constantly loomed large, and it is therefore fitting that the first authoritative monograph on the physiology and clinical manifestations of normal and abnormal hemostasis should have been written by this Marquette University investigator.

The book is distinguished by its thoroughness and clarity, and above all by its wisdom. Well and simply written, it fulfils a long-felt need in grouping together in separate chapters the many accumulated bits of knowledge regarding thrombin, prothrombin, thromboplastin, fibrinogen, platelets and anticoagulants. The references, which are unusually complete, are alphabetically grouped at the end of each chapter.

Discussions of physiologic principles are followed by chapters dealing with such clinical conditions as thrombopenic purpura, hemophilia and hypoprothrombinemia, and with the uses of heparin and dicoumarol. Although a thorough discussion and painstaking review of the literature distinguish these chapters, they suffer somewhat from the author's primary concern with the laboratory rather than with the clinic. Particularly with thrombopenic purpura and hemophilia there is too much reliance on the literature and on some of the author's "pet" theories, for example, a histamine disturbance in purpura and a simple thromboplastin defect in hemophilia. There is increasing evidence that idiopathic thrombopenic purpura is primarily a splenic dysfunction with remote, possibly hormonal, inhibition of platelet formation from megakaryocytes in the bone marrow. As regards hemophilia, the clearcut experiments of F. H. L. Taylor and his associates at the Thorndike Memorial Laboratory of the Boston City Hospital are dismissed with scant notice. Whether hemophilia is primarily a thromboplastin deficiency or an abnormality in the euglobulin fraction of the plasma is still not entirely settled; perhaps both groups of investigators are correct.

These criticisms are possibly captious, for the book is not only authoritative and thorough but respectful of the extensive literature and not unmindful of the historical roots of each particular subject. The format, typography and printing are quite in keeping with the general excellence of the work, which is completed by an appendix containing methods for determination of the coagulation time, bleeding time, clot retraction, platelet count, and levels of prothrombin and fibrinogen, together with methods for the assay of thromboplastin, thrombin and heparin.

The book is highly recommended for use in general hospitals and clinical laboratories. Collaboration with a clinical investigator might be desirable in a second edition.

First Aid to the Injured and Sick: An advanced ambulance handbook. Edited by Major Norman Hammer, M.R.C.S. Eighteenth edition. 16°, paper, 336 pp., with 313 illustrations. Baltimore: The Williams and Wilkins Company, 1941. $2.00.

The fact that this little volume is its eighteenth edition speaks well for its popularity. The first part of the book is devoted to the form and functions of the body. This section gives a clear and remarkably well-illustrated account of body structures in an extremely simple and concise manner.

The author states that air-raid first aid has been his special interest for the past five years, and the numerous illustrations of and directions for first aid show how well he has accomplished his task of explaining sound methods clearly and graphically to the students of this subject. The chapter on sprains, dislocations and fractures is particularly commended, as is the section on the first-aid treatment of hemorrhage and wounds. The newer treatments of burns and injuries from gassing are given careful attention.

The book will be of great value to all who would familiarize themselves with first-aid treatment.

(Notices on page x)

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NOTICES

ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

The fifty-first meeting of the Association of Military Surgeons of the United States will be held at the Bellevue-Stratford Hotel, Philadelphia, on October 21, 22 and 23. The program, essentially a symposium on war medicine, will be of vital and direct interest to medical officers, civilian physicians and scientists, as well as to the general public, and will be featured by first-hand reports of medical officers who have served in combat under a variety of climatic conditions. Other timely subjects will include air evacuation, parachute injuries, the physiologic aspects of high-altitude flying and dive bombing, tropical medicine, blast injuries, amphibious operations, submarine warfare, the complications of immersion and extremes of temperature, neurosurgical problems and rehabilitation. Besides general sessions, the program lists forum lectures and teaching panels, as well as extensive exhibits and a variety of motion-picture films.

NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, September 9 (the *first* Thursday rather than the *second* Thursday of the month), at 7:15 p.m. in the classroom in the Nurses' Residence. The subject will be "Oxygen Therapy." Dr. Esther E. Bartlett will be chairman.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 9

THURSDAY, SEPTEMBER 9

•10:00–11:30 a.m. Medical staff rounds. Peter Bent Brigham Hospital.

7:15 p.m. Oxygen Therapy. New England Hospital for Women and Children.

MONDAY, SEPTEMBER 13

•12:15–1:15 p.m. Clinicopathological conference. Peter Bent Brigham Hospital.

TUESDAY, SEPTEMBER 14

•12:15–1:15 p.m. Clinicoroentgenological conference. Peter Bent Brigham Hospital.

2:00–4:00 p.m. Myasthenia gravis clinic. Out Patient Department, Massachusetts General Hospital.

WEDNESDAY, SEPTEMBER 15

•12:00 m. Clinicopathological conference. Children's Hospital.

•Open to the medical profession.

SEPTEMBER 8–11. American Congress of Physical Therapy. Page 32, issue of July 1.

SEPTEMBER 9. Toxemias of Pregnancy. Dr. Duncan E. Reid. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

OCTOBER 6. Conference and Seminar in Legal Medicine. Page viii, issue of August 12.

OCTOBER 11–22. 1943 Graduate Fortnight of the New York Academy of Medicine. Page 32, issue of July 1.

OCTOBER 21–23. Association of Military Surgeons of the United States. Notice above.

(Books Received on page xiii)

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Brucellosis in Man and Animals. By I. Forest Huddleson, D.V.M., M.S., Ph.D., research professor in bacteriology, Michigan State College. Revised edition. 8°, cloth, 379 pp., with 42 illustrations and 36 tables. New York City: The Commonwealth Fund. 1943. $3.50.

The 1943 edition of this well-known treatise has been brought up to date, and more complete descriptions of the brucellosis organisms are given, as well as a detailed discussion of the recently developed simple and rapid method of determining the virulence.

War and the Doctor: Essays on the immediate treatment of war wounds. Edited by J. M. Mackintosh, M.D., chief medical officer, Department of Health for Scotland. 8°, cloth, 135 pp. Baltimore: William Wood and Company, 1943. $2.00.

This collection of short essays was first published in 1940, revised the same year, and reprinted from time to time. It is based on a series of lectures delivered by various physicians at the request of the British Medical Association. Chapters are devoted to fear neuroses, shock and hemorrhage, war injuries to the face and jaw, chest injuries, head injuries, the immediate treatment of air-raid injuries, first-aid instruction in wartime, and emergency surgery in the field.

A Guide to Practical Nutrition: A series of articles on nutrition, sponsored by the Committee on Nutrition and Deficiency Diseases of the Philadelphia County Medical Society. Edited by Michael G. Wohl, M.D., and John H. Willard, M.D. With an introduction by Morris Fishbein, M.D., editor of the *Journal of the American Medical Association.* 8°, paper, 98 pp. Reprinted from *Philadelphia Medicine,* 1941-1942.

This short manual is the composite work of a number of physicians and is divided into fourteen short chapters. It is written as a part of a program of public-health education and is intended for physicians. The first chapters discuss proteins, carbohydrates, fats and minerals, followed by diet in general and diet in pregnancy. There are chapters on nutrition in childhood and in older persons, vitamin deficiencies, vitamin B complex and riboflavin, and nutritional aspects of dental disease. The final chapter has to do with nutrition as a problem of war and public health. There is an appendix containing various food tables and charts.

A Manual of Clinical Therapeutics: A guide for students and practitioners. By Windsor C. Cutting, M.D., associate professor of therapeutics, Stanford University School of Medicine, San Francisco. 12°, cloth, 609 pp. Philadelphia and London: W. B. Saunders Company, 1943. $4.00.

This new manual is intended as a compact and practical guide for students, house officers and general practitioners. The drugs mentioned are almost entirely chosen from the *Pharmacopoeia of the United States,* the *National Formulary* and *New and Nonofficial Remedies.*

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ANESTHESIA — One-week course in continuous caudal anesthesia for obstetrics.

OPHTHALMOLOGY — Two-week intensive course starting September 27. Course in refraction methods October 11.

OTOLARYNGOLOGY — Two-week intensive course starting September 13.

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